GROWTH
Genetics & Hormones

Vol. 1 No. 1 March 1985

Growth Hormone Physiology and Pathophysiology: A Review

The complex system that encompasses the release and action of growth hormone (GH) includes many neurotransmitters, hormones, and organs. Among these are biogenic amines such as dopamine and serotonin in the brain; somatotropin-releasing hormone (SRH) and somatostatin or somatotropin-release–inhibiting hormone (SRIH) in the hypothalamus; somatotropin or GH in the pituitary; and insulin-like growth factors I (IGF-I) and II (IGF-II) in the liver and possibly in other organs. The mechanisms by which this complex system generates growth as a result of GH production and release from the pituitary are rapidly being elucidated.

One purpose of this article is to review the current concepts regarding these mechanisms, thus facilitating interpretation of the abstracts that are highlighted in this newsletter. The second goal is to briefly emphasize that more is known about the mechanisms involved in the secretion of GH and IGF than about the indications for treatment with GH.

A number of phasic changes in GH secretion are mediated by brain centers under the stimulus of bioamines. For example, dopamine is a stimulus to GH secretion. The arcuate nucleus, in particular, and possibly the ventromedial nucleus as well, respond by releasing SRH and SRIH. Both are transported from the hypothalamus via the portal system to the pituitary, where they attach to their respective receptors on the somatotrophs. Interestingly, SRIH, also referred to as somatotropin-release–inhibiting factor (SRIF) or somatostatin, is present in organ systems other than the brain (ie, the pancreas and gut). However, SRH has not been shown to be present normally in structures other than the hypothalamus. Three forms of SRH have been identified—one with 44, one with 40, and one with 37 amino acids. These forms are approximately equipotent. The first two have been identified in the hypothalamus.

The synthesis and release of GH in the somatotrophs are under the control of the cAMP system. Both synthesis and release are sensitive to calcium ion fluxes and diacylglycerol. Protein kinase-C, the putative phorbol ester receptor, also plays an important role in the stimulated secretory pathway for GH, as indicated by marked increases in GH release by anterior pituitary cells of rats following stimulation with the phorbol ester, phorbol-12-myristate-13-acetate. SRH, choleratoxin, and forskolin lead to cAMP accumulation in somatotrophs and stimulate growth hormone release; SRIF inhibits both actions of these secretagogues, and thus its action is also closely related to the cAMP system. As the pituitary portal blood concentrations of SRH and SRIF change, the serum levels of GH rise

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and fall in an intermittent pulsatile fashion.

The feedback mechanisms to control GH release are multiple and complex. For example, SRH can diminish its own secretion in the rat, as shown by Tannenbaum, who injected SRH in graded doses into the cerebral ventricles of rats. Increasing doses given in this manner led to a dose-dependent inhibition of GH secretion. This profound effect was not due to SRIF secretion, as shown by the inability of the antiserum to SRIF to reverse the suppression of GH release. Thus, SRH can affect its own secretion by means of an ultrashort negative feedback loop mechanism.

In addition, SRH produces negative feedback at the somatotroph when there is lengthy exposure to the peptide. Pretreatment of anterior pituitary cell cultures from rats with SRH resulted in decreased cAMP and GH concentrations in these cells when the cells were reexposed to SRH.

Insulin-like growth factors also are involved in the feedback control of GH secretion. When placed in the cerebral ventricles, IGF-I causes a profound decrease in the spontaneous intermittent secretion of GH in rats. This action may occur through the release of SRIF. Berelowitz et al demonstrated that IGF-I directly stimulates the acute release of SRIF from rat hypothalamic fragments in culture.

Growth hormone also plays a feedback role in GH secretion. Berelowitz et al noted that GH acts at the hypothalamus to stimulate both the synthesis and release of SRIF. Abrams, Grumbach, and Kaplan demonstrated in humans that GH injections given every six hours for six days diminished GH release by the pituitary when insulin was given eight hours after the last GH injection. It was not ascertained whether this was a direct effect of GH or an indirect effect through somatomedin generation. In summary, there is a complex series of negative feedback loops that control the tonic and phasic secretion of GH.

After GH is released into the circulation, it travels to the liver and other tissues, including chondrocytes in growing cartilage. In the liver, and possibly in cells of other tissues, GH stimulates the production of IGF-I and IGF-II. These growth factors, homologues of the proinsulin molecule, have biologic effects that are qualitatively similar to those of insulin. Although IGF-II possesses more insulin-like activity than IGF-I, neither factor reacts with anti-insulin antibodies. The molecular weight of each is about 7,500 daltons, and the factors resemble proinsulin in that about 50% of the amino acid residues in the A and B chains are identical with the corresponding sequences in human proinsulin. Radioimmunoassays specific for each of these have been developed, and a radioreceptor assay for IGF-II is performed in several laboratories.

Both IGF-I and IGF-II are under GH control, since concentrations of both have been reported to fall with GH deficiency. There is no question that IGF-I uniformly falls with GH deficiency; however, Bucher et al reported that IGF-II levels were normal in most patients with GH deficiency. Only IGF-I rises above adult values with GH excess. Moreover, the concentration of IGF-I rises slowly throughout childhood and peaks during adolescence at values that are two to three times higher than preadolescent and postadolescent values. IGF-II increases sharply after birth and normally remains constant throughout life. The insulin-like growth factors also differ in their growth-promoting activity: IGF-I is a potent sulfation factor, but IGF-II is weak in this regard.

IGF-I itself is probably essential to growth, although the possibility that GH may act directly on chondrocytes has not been totally excluded. Recent studies have suggested a direct effect on the longitudinal bone growth process by GH to the epiphyseal cartilage growth plate of hypophysectomized rats. Even the generation of IGF-I, however, does not guarantee normal growth. In certain humans with a GH-deficient–like phenotype, GH and IGF-I concentrations are normal or elevated, but growth does not occur normally. Therefore, the cell must be able to accept IGF-I and translate its presence into action with synthesis of DNA, leading to cell multiplication (see page 12, Bierich et al: *Eur J Pediatr* 1984;142:186).

It is apparent that many steps are required for the synthesis and secretion of GH, and in the synthesis and action of insulin-like growth factors. Consequently, the physician evaluating a child with short stature, delayed bone age, and the clinical appearance of GH deficiency may be perplexed by the results of tests for GH secretion. Growth hormone deficiency may be complete, partial, or even transient as in children with psychosocial short stature. The child being evaluated may even secrete normal or increased amounts of GH but not generate IGF-I normally.

Therefore, IGF-I (somatomedin-C) determinations become important adjuncts in the evaluation of such patients. However, as mentioned previously, there are some patients who secrete GH and IGF-I normally, but who are unable to translate the presence of IGF-I into action on cell growth and multiplication. Consequently, consultation and sharing of knowledge among physicians interested in growth problems is an essential component of appropriate diagnosis and treatment.

Treatment of patients with obvious GH deficiency is straightforward. However, treatment of patients who have a GH-deficient–like phenotype—but who generate GH in at least certain testing situations—is not straightforward. Growth hormone may be effective in some such children, but not in others. Appropriate controlled studies need to be done to determine which children with a GH-deficient–like phenotype will increase their growth rates and, possibly, their ultimate heights.

Until such time as these studies have been done and we know as much about the therapeutic aspects of GH as we know about the physiologic aspects as outlined above, cautious prescribing of GH is judicious.

Alan D. Rogol, M.D., Ph.D
Robert M. Blizzard, M.D.

References supplied upon request to authors.

A Letter to Our Readers

Dear Colleague:

The Editorial Board is pleased to introduce the inaugural issue of *Growth, Genetics, and Hormones*, a publication for academicians and practicing physicians who are interested in these important areas of medical practice. We are pleased to welcome you as a reader and invite you to participate as a reader and as a correspondent.

Normal and abnormal growth, genetically determined conditions, and the overall development of children are important aspects of pediatric practice. Hormonal production is essential in growth and development. It is probable that these areas will assume even greater prominence because pediatricians are showing greater interest in growth and development as immunizations and antibiotics diminish the incidence of infectious disease, as greater numbers of children with leukemia and other cancers enter sustained remissions, and as growing numbers of handicapped infants with congenital anomalies survive.

It is also well recognized that the literature concerning these topics is voluminous. Therefore, *Growth, Genetics, and Hormones* was developed, primarily, to provide a close look at current—and often controversial—topics in endocrinology, genetics, and metabolism and their potential clinical applications. To ensure that this goal is met now and in the future, several nationally and internationally respected authorities in genetics, endocrinology, anthropometrics, pediatrics, pharmacology, and metabolism have agreed to serve on the Editorial Board.

The eminent investigators who have agreed to serve as Associate Editors are: Dr. Jürgen Bierich of the University of Tübingen, West Germany; Dr. Judith Hall of the University of British Columbia Medical School; Dr. Fima Lifshitz of Cornell University School of Medicine; Dr. David Rimoin of the University of California at Los Angeles; Dr. Alan Rogol of the University of Virginia School of Medicine; and myself. You will meet each of the Board members in the early issues of *Growth, Genetics, and Hormones* (see page 5 of this issue).

The editorial content of this quarterly publication was chosen with your interests in mind. This issue, for example, features an article about the incidence of growth hormone deficiency, a review of growth hormone physiology and pathophysiology, and a summary of a recent conference concerning the psychosocial aspects of growth delay. These are scientific, timely, and representative of the topics that *Growth, Genetics, and Hormones* will address.

Abstracts of pertinent articles and reports will appear in each issue. In the future, the abstracts will serve as "mini reviews" and integrate multiple reports on a particular topic.

An Editor's Column will be a regular feature of future issues. You are invited to correspond with the Editorial Board. Such correspondence will be included whenever possible and will receive an open reply when indicated.

To help you keep up with major developments in pediatrics, genetics, and endocrinology, a calendar of meetings and postgraduate courses will appear in each issue. You are invited to advise us of meetings that you think pertinent for publication.

We are pleased to present this inaugural issue to you. We welcome your readership and look forward to hearing from you about *Growth, Genetics, and Hormones*. We would also appreciate your filling out the enclosed reply card to let us know of your initial interest.

On behalf of the Editorial Board:
Sincerely,

Robert M. Blizzard, M.D.
Professor and Chairman
Department of Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia

The Incidence of Growth Hormone Deficiency: Does Anyone Know?

Much attention is being directed by clinical investigators, pharmaceutical firms, geneticists, and pediatric endocrinologists to the incidence of growth hormone (GH) deficiency. Investigators are interested in this because the incidence dictates the number and type of studies that can be performed. Pharmaceutical firms are interested because the incidence will determine the market for the sale of native or DNA-recombinant hormone. Geneticists are interested because of the multiple biochemical or anatomic lesions that might be associated with GH deficiency. Pediatric endocrinologists are interested because they are the physicians primarily responsible for the diagnosis and treatment of GH deficiency.

No one knows for certain what the actual incidence of GH deficiency is. The reason for this is related to our inability to define GH deficiency itself. According to a study by Vimpani et al (*Brit M J* 1977;2:247), GH deficiency is present if the GH concentration is <9 ng/ml to two stimuli; the height is >2.5 SD below the mean height for age; and the height velocity falls at or below the 25th percentile for chronological age. The prevalence of idiopathic GH deficiency in Scotland, according to Vimpani's study, is approximately 1:5,000 (4,000 to 6,500) births. Extrapolating from this ratio, there would be 14,500 such patients under 21 years of age in the United States.

This incidence, however, does not take into account those patients with organic hypopituitarism resulting from tumors of the hypothalamus or pituitary, or from other lesions, such as histiocytosis X, that produce GH deficiency. A review of several articles suggests that one case of organic hypopituitarism occurs for every four cases of obvious idiopathic GH deficiency. During the past ten years in our own clinic at the University of Virginia Medical Center, 84 patients with idiopathic GH deficiency and 36 patients with craniopharyngiomas or other causes of organic hypopituitarism have received GH. If our figures are representative, approximately 20,000 cases of hypopituitarism exist nationwide in children less than 21 years of age.

However, there are other questions that should be considered before we accept this figure even as an approximation. What about patients with partial GH deficiency? What about patients who have what could be an immunologically active but biologically inactive hormone? What about other children who have the phenotype of GH deficiency and low somatomedin-C determinations, but who have significant levels of GH when tested? What about the patients who have severe constitutionally delayed growth and adolescent development?

There are many patients who might be considered GH deficient if one takes these patient groups into account. Patients with partial GH deficiency include those like the seven patients described by Spiliotis (see page 8 of this issue), who are believed to have GH neurosecretory dysfunction. The criteria consistent with the clinical picture of GH deficiency were present in these patients, although they had GH concentrations greater than 10 ng/ml when tested with pharmacological agents. Compared with normal-sized children, these patients had decreased integrated concentrations of GH over a 24-hour period and a decreased number of GH secretory episodes during the 24 hours. They responded to GH injections with growth rates comparable to those patients who were classified as GH deficient. Rudman et al (*N Eng J Med* 1981;305:123), Hayek et al (*J Peds* 1981;99:868), and others have described similar patients, although integrated concentrations of GH have not always been determined. The patients of Rudman et al and Hayek et al also have responded to GH with growth comparable to that observed in patients who are unequivocally GH deficient.

The problem of determining the incidence of GH deficiency may even be more complex than cited above. Patients with constitutional delay of growth may have a relative GH deficiency (Bierich and Polthoff, *Monatsschr Kinderheilkd* 1979;127:561), as determined by low nocturnal GH levels, when compared with children without constitutional growth delay. If these patients have GH deficiency, it may be transient and is often reversed when adolescence begins. Of interest is the observation that 10% to 20% of patients believed to have GH deficiency prepubertally, and who have been treated with GH, do not have GH deficiency as adults. This percentage range was determined from our studies of more than 60 adults who were treated with GH as children because they were found to be GH deficient by pharmacological testing. Gourmelen et al have also drawn attention to transient partial GH deficiency in prepubertal children with growth delay (*Pediatr Res* 1979;13:221).

Thus, it bears repeating that no one really knows the actual incidence of GH deficiency. In the United States, the incidence is undoubtedly much greater than the 14,500 cases estimated from the data of Vimpani et al. Even discounting patients with constitutional growth delay, there are probably 20,000 or more American children with complete or relative GH deficiency. Unfortunately, the tedious nature and expense of determining integrated concentrations of GH over a 24-hour period will prevent the diagnosis of GH deficiency in many patients who have the phenotype of GH deficiency, but who respond normally to provocative stimuli with GH release.

At this time, it should be emphasized that methods other than those currently available, including therapeutic trials, must be designed to determine the incidence of GH deficiency as a cause of short stature. Therefore, it is essential that we devote special attention in the next few years to research concerning the incidence, diagnosis, and treatment of GH deficiency.

Robert M. Blizzard, M.D.

Meet the Editorial Board Chairman:

Robert M. Blizzard, M.D.

Dr. Blizzard is Professor and Chairman of the Department of Pediatrics at the University of Virginia School of Medicine in Charlottesville, Va. He also serves as Associate Director of the Clinical Research Center there. Before coming to Virginia, Dr. Blizzard was Chief of the Division of Pediatric Endocrinology at Johns Hopkins Hospital in Baltimore. During this time he was also Associate Professor of Pediatrics and, later, Professor of Pediatrics at The Johns Hopkins University School of Medicine.

Educated at Northwestern University in Evanston, Ill, and Northwestern University Medical School in Chicago, Dr. Blizzard has been involved in pediatrics and pediatric endocrinology since his graduation more than 30 years ago. After his internship and residency at the Raymond Blank Memorial Hospital for Children in Des Moines, he became a fellow in pediatric endocrinology at the Harriet Lane Home and Johns Hopkins Hospital. He then joined the medical faculty at Ohio State University in Columbus, serving at the same time as Chief of the Endocrine and Metabolic Unit at The Children's Hospital of Columbus.

Dr. Blizzard was President of the Human Growth Foundation in 1969-1970 and President of the Lawson Wilkins Pediatric Endocrine Society for 1974-1975. A former Director of the National Pituitary Agency of the National Institutes of Health (NIH) in Bethesda, Md, he still serves on its medical advisory board and as a special consultant to the NIH.

Dr. Blizzard has extensively studied the role of growth hormone in patients with normal and abnormal growth. He has authored or coauthored 160 articles and coauthored, edited, or contributed to 19 textbooks on this and related subjects.

In Future Issues

Introduction of the other members of the Editorial Board

Assessing the Efficacy of Growth-Promoting Substances in Children: Methods and Problems
by James Tanner, M.D.

Nutrition, Growth, and Growth Failure
by Fima Lifshitz, M.D.

Associate Editor:

Fima Lifshitz, M.D.

At present, Dr. Lifshitz is Professor of Pediatrics at Cornell University Medical College in New York. He is also Associate Director of the Department of Pediatrics; Chief of the Division of Pediatric Endocrinology, Metabolism, and Nutrition; and Chief of Pediatric Research at North Shore University Hospital in Manhasset, NY.

A native of Mexico City, Dr. Lifshitz graduated from that city's Yavne College and the National University of Mexico School of Medicine. After graduation, he served an internship at Children's Mercy Hospital in Kansas City, Mo, and a residency in pediatrics at the University of Kansas Medical Center in Kansas City, Kan. He then became a fellow in endocrinology and nutrition in the pediatric research training program at the Children's Medical and Surgical Center at Johns Hopkins Hospital in Baltimore. Returning to Mexico City, he served for two years as physician-investigator at the Hospital de Pediatria.

Since 1970, Dr. Lifshitz has been a visiting professor at numerous institutions in the United States, Israel, Egypt, South America, and China. A prolific author, he has written extensively about metabolic disease and gastrointestinal disturbances and how these conditions produce altered growth patterns. He has authored or coauthored 82 journal articles, 42 textbook chapters and review articles, and 107 abstracts and other short communications. He has also edited eight textbooks.

His writings and research efforts have contributed significantly to the understanding of carbohydrate intolerance in diarrheal disease, vitamin D–dependency rickets in children on long-term anticonvulsant therapy, experimental magnesium deficiency, and intestinal transport of vitamins and minerals in experimental malnutrition and diarrhea.

Address for Correspondence
Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

The Psychosocial Aspects of Growth Delay

During the past century, studies of the effects of short stature on personality development and social function have been plagued by anecdotal reporting and lack of objective, reliable testing procedures. This has led to inconsistent and often conflicting results. However, with the possibility of an unlimited supply of growth hormone (GH) for therapeutic use in the near future, there is an urgent need for sound scientific data on which to base future therapeutic decisions.

To address this problem, approximately 150 psychologists, sociologists, social workers, psychiatrists, endocrinologists, parents, and patients gathered in Washington, DC, this past October to attend a symposium on the psychosocial aspects of growth delay. Brian Stabler, Ph.D., and Louis Underwood, M.D., both of the University of North Carolina at Chapel Hill, served as moderators of 13 formal presentations and discussion periods that dealt with the behavior patterns, cognitive functioning, psychological status, and social integration of persons with GH deficiency, constitutional short stature, Turner's syndrome, chondrodystrophies, and deprivation dwarfism.

The issue of whether height affects academic achievement was addressed by Drs. C. Holmes (Des Moines), R.A. Richman (Syracuse, NY), P.T. Siegel (Ann Arbor, MI), and D. Young-Hyman (Baltimore). They all reported that actual school performance levels are discouraging, despite a normal range of intelligence quotients (IQs) in children with hypopituitarism and constitutional short stature. Dr. Holmes suggested that this may be related, in part, to decreased social competence in the mid-teen years. Dr. Young-Hyman pointed out that perhaps not enough attention had been paid to differentiating measures of personality adjustment from measures of social competence—eg, peer relationships and participation in extracurricular activities.

Dr. Richman found no severe psychological problems (as determined by a variety of psychological tests) in these children. However, he suggested that subtle personality traits, such as shyness, low self-esteem, and increased internalization of complaints, as well as specific parental attitudes, such as increased permissiveness and decreased communication, may contribute to the children's poor school performance. Dr. Siegel reported that the pattern of poor academic performance was due, in part, to specific unrecognized cognitive defects, ie, learning disabilities. She noted, however, that in her group of GH-deficient subjects, 50% had at least one high-risk perinatal factor such as asphyxia or breech delivery, which could also have contributed to the cognitive defects.

In contrast to these four studies, R. Rosenfeld and D. Wilson of Stanford University reported a positive relationship between height and IQ. Their finding was based on a very large sample of normal children from the National Health Examination Survey. Rosenfeld and Wilson hypothesized that about 4% of the variance of IQ in the general population could be accounted for by height.

The unrecognized cognitive defects described by Dr. Siegel in the group of children with GH deficiency were underscored by Drs. H.C. Steinhausen (Berlin) and J. Downey (Columbia University) in their discussions of the perceptual defects in women with Turner's syndrome. The minor psychiatric problems experienced by the majority of these women were similar to those in an age- and size-matched group of females with constitutional short stature, suggesting that these problems are directly related to stature.

To assess the psychosocial benefit of increasing final adult height, Drs. R. Clopper (Buffalo), A. Johanson (Charlottesville, VA), and H. Dean (Winnipeg, Manitoba) described the long-term social outcome of GH-deficient adults treated with GH during childhood. In the three populations studied, the educational records were average but the rates of employment and marriage were low. The reasons for this overall social maladjustment remain speculative. A significant proportion of these subjects expressed greater concern over their immature physical appearance than their short stature.

Dr. D. Rotnem (Yale University) discussed the pivotal role of family interaction in the ultimate psychosocial outcome of children with all forms of growth delay. She addressed the problems of parenting a short child, specifically in terms of the ambiguity of the child's size *v* age. She outlined various ways in which parents have learned to cope with the problem and identified risk factors associated with poor capability: lack of consistency, conflict between parents, ambivalence, and guilt.

Drs. D. Drotar (Chicago) and C. Annecillo (Baltimore) described poor psychosocial adaptation as not only a result, but also a major cause, of growth delay in infants.

One of the recurring themes of the meeting was the continued inconsistency in results obtained from the currently available battery of psychological tests. These tests do not appear to be sufficiently sensitive to identify subtle social problems. There was general agreement among the conferees that there are serious psychosocial problems associated with growth delay, and concern was expressed that these problems remain ill-defined. In his after-dinner speech, Dr. L.P. Sawisch noted that the limited attention paid to growth-related psychosocial problems is deeply rooted in society's preoccupation with height. It is therefore difficult to study these problems in isolation. The frustration expressed by the investigators regarding inadequate research tools, study design, and testable hypotheses was echoed by the parents and patients. Children and parents also perceived a lack of sensitivity on the part of the health-care and education systems. Parents felt that school personnel in particular were ill equipped to deal with the psychological needs of children with delayed growth and suggested that health educators be actively involved in programs to increase public awareness of growth-related problems.

Among the questions posed by

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The Psychosocial Aspects of Growth Delay

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the participants at the end of the conference were the following: In the study of psychosocial issues should all persons with short stature be considered as a group or divided into separate diagnostic categories? Should they be viewed as a group with a chronic disease and compared with other groups of children with chronic medical disorders? Is it relevant to study groups to compare early *v* late adolescence and late adolescence *v* early adulthood? What is the best way to explore and control for varying degrees of family functioning? What is the most appropriate way to develop more reliable, sensitive, and standardized test procedures? It seems likely that the rapid pace of development in biotechnology and the future commercial availability of GH will provide the impetus for a new era in scientific endeavor to answer these important social questions.

Heather J. Dean, M.D.
Associate Professor of Pediatrics
Faculty of Medicine
University of Manitoba
Winnipeg, Manitoba. Canada

Dr. Dean is a guest contributor for this issue. A highly respected pediatric endocrinologist with a special interest in the psychological aspects of growth disorders, Dr. Dean was among the speakers at the symposium reported above.

Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

Use of a Two-Site IRMA for GH in Identifying Children With GH-Dependent Growth Failure

Blethen and Chasalow compare the circulating growth hormone (GH) concentrations in adults of normal stature, endocrinologically normal short children with normal growth rates, and children with GH-dependent growth failure.

They used both the standard double antibody radioimmunoassay (RIA) method with a polyclonal guinea pig antiserum and a new immunoradiometric assay (IRMA). The former employs the standard National Hormone and Pituitary Program reagents and the latter uses two different monoclonal antibodies prepared against human growth hormone (hGH) (Hybritech, San Diego, CA). One antibody is covalently linked to a sepharose bead and the second is labeled with ^{125}I. These monoclonal antibodies were selected for IRMA on the basis of antibody competition for GH binding with the ^{125}I-labeled antibody. This assay is successful because each antibody binds to the GH molecule at a different epitope. The IRMA procedure is simpler and less time-consuming than the RIA technique.

The theoretic advantages of the IRMA method are: (1) linearity; (2) a relatively stable coefficient of variation over a greater range of antigen concentrations than in the classical RIA techniques; and (3) improved sensitivity and precision. With the use of monoclonal rather than polyclonal antibodies, several additional benefits are derived: (1) the amount of antibody is unlimited so that one can generate a very high capacity solid phase antibody system; and (2) since only a single type of antibody (selected for high affinity) is attached to the solid phase support, higher antigen concentrations can be tested.

The investigators sought to compare the results of circulating GH levels in normal adult volunteers, normal short children, and children with GH-dependent growth failure to determine if children in the last group (whose pharmacologic stimulation tests for GH secretion were normal) had an immunologically distinguishable circulating GH species. Since samples that had no measurable GH by RIA were always unmeasurable with IRMA, samples for the IRMA were selected from samples with GH detectable by RIA.

When purified hGH was added either to human serum or the kit "zero calibrator," there was a strong correlation between the values found by RIA and IRMA (slope of the regression line = 0.86). In both normal individuals and children with GH-dependent growth failure, the ratio of IRMA-GH to RIA-GH was not affected by the time of sampling relative to the peak. The mean IRMA-GH to RIA-GH ratios were 0.48 ± 0.02 for normal subjects (slope = 0.62) *v* 0.35 ± 0.001 (slope = 0.39) for subjects with GH-dependent growth failure. These values are significantly different at $P<0.001$.

These results indicate that both assays measured the authentic material with approximately equal effectiveness. For the normal group the slope of the regression line was less, indicating that there were differences in the folded structure of pituitary and circulating GH. However, the slope of the assay for those children with GH-dependent growth failure was even lower, indicating that their circulating forms of GH differed from those of normal subjects. The latter group of children is precisely the group that responded to exogenous replacement of GH.

Blethen SL, Chasalow FI: *JCE&M* 1983;57:1031.

Editor's comment—These data are exciting and, if confirmed, could materially aid physicians in deciding which children might respond to exogenous GH therapy. At present, some of these patients are considered to be at variance from normal, since they have normal levels of GH following physiologic or pharmacologic stimuli to GH secretion. The simple expedient of assaying their circulating levels of GH in two separate assays may enhance our knowledge of the syndrome of GH-dependent growth failure and target a group for a therapeutic trial with GH.

Neurosecretory Dysfunction: A Treatable Cause of Short Stature

Studies presented in this article indicate that there is a group of short children who, although not growth hormone (GH) deficient by classic definition, do not secrete an adequate amount of GH during a 24-hour period to grow normally. Seven children (7.4 to 15.5 years of age) so classified met criteria consistent with GH deficiency: height less than first percentile, growth velocity <4 cm/yr, bone age at least 2 years behind chronological age, and low somatomedin-C concentrations for age, except that there was a GH peak >10 ng/ml to provocative testing. These children are classified as children with neurosecretory dysfunction (NSD). Twenty-four–hour integrated concentrations of GH (ICGH) (samples withdrawn every 20 minutes) were compared with concentrations from 16 GH-deficient children and 22 controls.

All children with NSD had nocturnal GH peaks of 10 ng/ml or greater. Six of the 16 GH-deficient patients also had nocturnal peaks of 10 ng/ml or greater. These data indicate the poor correlation between pharmacologic testing and nocturnal peaks of GH in GH-deficient children and the poor correlation between pharmacologic testing, nocturnal peaks, and ICGH in children with NSD.

	N	ICGH	No. of peaks 24 h	Area under curve	Mean per amplitude
Controls	7	5.4 ± 0.5 ng/ml	6.4 ± 0.3	129 ± 14 U	17.0 ± 1.4
GH deficient	16	1.6 ± 0.2 ng/ml	1.9 ± 0.5	26 ± 6 U	9.0 ± 2.2
NSD	22	2.1 ± 0.3 ng/ml	3.9 ± 0.6	42 ± 5 U	9.3 ± 1.2

Six of the seven patients with NSD responded to GH treatment (0.07 U/kg body weight three times weekly) nearly as well as the GH-deficient patients (a mean change in growth rate of 4.1 *v* 5.4 cm/yr).

In addition, the authors observed that nocturnal GH peaks in many of the children who manifested these peaks occurred in all stages of sleep except stage 4. In fact, the nocturnal GH peak may occur during another stage of sleep or in a subsequent period of stage 3 or 4. Interestingly, these investigators also found no differences in ICGH or patterns of GH secretion in children of various Tanner stages of sexual development. This is in accord with previous studies of some investigators (Thompson et al: *JCE&M* 1972;35:334), but not in accord with studies by Howse et al (*Clin Endocrinol* 1977;6:347), who suggested a pubertal increase in GH secretion based on five-hour nocturnal sampling in several short children.

As a result of these observations, the authors suggest that there is a spectrum of GH neurosecretory abnormalities ranging from absolute deficiency to a problem in GH regulation not readily identified with provocative testing. They also suggest that these abnormalities are manifested by reduced number and or amplitude of pulses, not readily identifiable with GH-stimulation tests, and that a majority of these patients respond to GH therapy with significant and sustained growth.

Spiliotis BE, August GP, Hung W, et al: *JAMA* 1984;251:2223.

Editor's comment—Spiliotis et al have demonstrated convincingly the points made in their report. It is apparent that not all patients with GH deficiency can be demonstrated by utilizing pharmacologic testing for GH release. The dilemma regarding the criteria for diagnosis of GH deficiency is emphasized from the data presented. Although the ideal method of diagnosis is to perform integrated concentrations of GH over 24 hours, this is impractical except in the research setting. These data emphasize the fact that it is difficult to determine the incidence of GH deficiency because it depends upon the criteria used to make the diagnosis.

Precocious Puberty After Hypothalamic and Pituitary Irradiation in Young Children

R. Brauner and co-workers at the Hôpital des Enfants-Malades in Paris report that six of 29 children treated with irradiation before seven years of age for medulloblastoma or other head and neck tumors, or for acute lymphoblastic leukemia, developed precocious puberty. Most developed precocious puberty within 30 months of irradiation therapy. Five had associated growth hormone (GH) deficiency. This combination of sexual precocity and GH deficiency produces short stature (136.7 cm, 143.5 cm, and 145 cm in the three patients whose heights were reported) in adulthood. It is important to consider that such children are at high risk for having very short adult stature, and require specific treatment of precocious puberty combined with GH therapy when a deficiency of this hormone is demonstrated.

Brauner R, Czernichow P, Rappaport R: *N Eng J Med* 1984;311:920.

Editor's comment—More and more children with tumors are surviving following irradiation therapy. This will increase the incidence of organic hypopituitarism and increase the use of GH as a therapeutic agent. Studies using luteinizing-hormone–releasing-hormone analogue in conjunction with human growth hormone are being conducted at the University of Virginia, Boston Children's Hospital, Massachusetts General Hospital, and the University of California, San Francisco, by R.M. Blizzard, J. Crigler, J. Crawford, and S. Kaplan, respectively. Physicians who encounter patients with GH deficiency accompanied by normal adolescent sexual development, and who are going to be unacceptably short, are urged to contact these investigators.

Laron Type Dwarfism (Hereditary Somatomedin Deficiency): A Review

Laron type dwarfism is a syndrome of familial dwarfism that is indistinguishable from isolated growth hormone (GH) deficiency except that patients have normal or elevated GH concentrations. The syndrome was described by Laron et al in 1966.

In the current review, Laron tabulates 72 cases. Many are non-Jewish. The birth weight, known in 21 cases, was >2,500 g in 18, and the birth length was more than 2 SD below the mean in ten of 16. Pregnancies and deliveries were unremarkable. Approximately 50% had skeletal or mesenchymal anomalies, none of which was life threatening.

Development in children with Laron type dwarfism is generally slow: many sit only after the age of 1 year and walk after 18 months. Fontanel closure occurs between 3 and 7 years. Symptoms of hypoglycemia and high-pitched voice are also characteristic. With the passage of time, the acromicria and disproportion between the face, with its saddle-nose, and the cranium become more apparent. The teeth are discolored, defective, and crowded. Growth is slow, with males reaching ultimate heights of 119 to 142 cm and females, 108 to 136 cm. Surprisingly, the upper/lower ratios are more than 2 SD above the mean, indicating that the limbs are short in comparison to the trunk. After puberty, the skin assumes a prematurely aged appearance. The genitalia in affected children and adults are very small, and pubertal development is slow. Menarche occurs between 13 and 18 years of age and ejaculation between 17 and 21 (compared to a normal mean of 13½ years).

Skeletal age is delayed. By x-ray analysis, the long bones are small and delicate, the sella is of normal size, and the facial bones are small in comparison to the cranium. The head consequently appears enlarged, but it is not (on the basis of standard measurement). Glucose intolerance is present even when hypoglycemia and hypoinsulinemia occur. Growth hormone levels often are elevated, but are suppressed normally with glucose. Serum somatomedin-C (Sm-C) concentrations are low, and do not increase after GH injections, although 50% of patients have an increase in free fatty acids. Nitrogen retention and hypercalcuria are minimal following GH administration.

No neurologic deficits were observed in these patients, and pneumoencephalograms were normal. IQ scores were strongly skewed toward the lower part of the curve (mean IQ = 82.1). Visual-motor coordination was uniformly poor. The parents regarded their own and their children's lives as ruined, since no remedial treatment exists for Laron type dwarfism. School was a negative experience for these children.

The etiology is believed to be related to the hGH receptors, since liver cell microsomes from these patients do not bind hGH normally, although insulin binds normally. Consequently, Sm-C is not generated.

Laron Z: *Advances in Internal Medicine and Pediatrics*. Heidelberg, Springer-Verlag, 1984, p 118.

Editor's comment—Laron et al have clarified the etiology and provided additional information about the syndrome. Treatment with Sm-C (IGF-I) might be effective. Unfortunately, adequate quantities are not currently available to test this hypothesis.

Height and Weight Status of Indo-Chinese Refugee Children

Pediatricians and other health practitioners who deal with children have no guidelines with which to evaluate the growth or growth potential of refugee children. The absence of such guidelines becomes problematic when one tries to determine if growth retardation exists in a particular child (which, in itself, would indicate that a search should be made to determine a cause). This report attempts to supply the needed information, and succeeds partially.

Height and weight measurements were obtained from 1,650 children residing in Laotian and Cambodian refugee camps and in areas surrounding these camps. Reference tables that are available from China, Thailand, and the United States were also used. The mean weights and mean heights for age of the groups studied are approximately 2 SD below US means, but there is variation.

These studies are inadequate because they are not randomized, as readily stated by the authors. To what extent catch-up growth may occur in refugee children remains to be determined. Evidence that nutrition plays a role was presented in one study in which the heights and weights of children from upper-class and professional backgrounds were compared to American standards. The mean heights and weights more nearly approached the US standards than the heights and weights found in refugee children.

Olness K, Yip R, Indritz A, et al: *AJDC* 1984;138:544.

Editor's comment—While these studies are limited, they are of value. We practitioners can assume with some justification that the normal growth curves for refugee Oriental children are approximately 2 SD below US curves.

	Height (SD)	Weight (SD)
US reference	0	0
Chinese urban	−0.8	−0.8
Chinese rural	−1.4	−1.3
Thai reference	−1.3	−1.8
Khmer refugee	−1.8	−1.8
Lao refugee	−2.1	−2.2
Thai village	−2.3	−1.9

Report of the Conference on Uses and Possible Uses of Biosynthetic hGH

In a society that values tallness, enormous pressure will be put on physicians to prescribe human growth hormone (hGH). The pressure will come from parents whose children are not fulfilling parental expectations in sports, social interactions, and academic achievement. Physicians will determine whether to prescribe hGH to children who are short because of normal genetic variation. They will be forced to decide whether to tamper with normal children in the hope of making them "better." Is it ethical to administer hGH to short children who are probably not growth hormone (GH) deficient according to current criteria? Will such treatment produce taller or better adults? What are the possible adverse side effects? How will misuse be prevented?

These considerations were addressed by 50 experts at a conference in late 1983 on the uses and possible uses of DNA-hGH. The conferees were asked to address the full spectrum of concerns about uses and abuses of hGH. Underwood summarized the conference findings in an editorial for the *New England Journal of Medicine*.

At the conference, one group addressed the question of how to distinguish partial GH deficiency. Provocative tests are not always reliable in determining whether insufficient GH is the cause of limited growth, since some patients with partial GH deficiency release significant amounts of GH when tested with pharmacologic agents. Participants discussed the increasing interest in measuring serum GH levels under physiologic conditions. Data are insufficient at present to permit judgment of optimal times, duration, and methods of measurement. The participants agreed that somatomedin-C concentrations are sometimes helpful in diagnosis if used in conjunction with other tests. Low values must be confirmed by GH testing before the diagnosis of GH deficiency is made, and low values in young children must be interpreted cautiously.

The terms used to describe short stature were also discussed: normal variant short stature, GH-dependent growth failure, and the syndrome of immunoreactive-bioinactive GH are poor terms.

The potential complications of glucose intolerance, hyperlipidemia, and possible acceleration of the atherosclerotic process with GH administration were considered. The conferees recommended that an epidemiologic survey of possible late-appearing side effects be undertaken in patients who have been or are being treated with hGH.

The consensus of the conferees was that there is an urgent need for therapeutic trials to determine the effect of GH in short children who do not have GH deficiency. It was deemed ethical to administer GH to such children under a controlled research study. Because no mechanism for direct regulation of prescribing hGH is available, it was agreed that the most effective way to avoid abuses is through the education of physicians and the public.

Underwood L: *N Eng J Med* 1984; 311:606.

Editor's comment—The above abstract is brief, and the interested reader is encouraged to review the entire report. Consideration of this well-reasoned editorial by all physicians who will be prescribing hGH for any cause is imperative.

Comparison of Physiologic and Pharmacologic Assessment of GH Secretion

Siegel et al evaluated and compared growth hormone (GH) release to arginine (ATT), insulin (ITT), and sleep. Samples were drawn every 30 minutes between 11:00 PM or midnight and 6:00 AM via an indwelling catheter. Sixty-two short children (53 males and nine females) were evaluated. Twenty (32%) failed to respond significantly to either test (maximal GH, <3.5 ng/ml). Surprisingly, only 14 of these 20 were classified by the authors as truly and permanently GH deficient. The other six were patients with constitutional growth delay, psychosocial dwarfism, and hypogonadotropic hypogonadism. Five subsequently had normal peaks during sleep.

Thirty-three (53%) of the 62 responded normally to both the pharmacologic and physiologic tests. Eight (13%) had abnormal responses to pharmacologic testing but normal responses to physiologic testing (mean peak GH = 19.0 ± 2.0 ng/ml). Seven of these eight were growing 5.0 cm/yr or more and were believed to have constitutional growth delay. Only one patient (<2%) failed to respond to physiologic stimuli but responded to pharmacologic stimuli.

These results confirm previous studies that show there is often a discordance in the GH response in normal individuals who are tested with arginine- and insulin-induced hypoglycemia. The authors state that the responses to the two tests were concordant in 43 of 62 patients (69%). However, if the 28 patients who responded to neither ATT nor ITT are removed, the authors found that only 23 of 42 patients (55%) who responded did so to both stimuli.

These studies verified previous reports that more than one pharmacologic test must be used to diagnose GH deficiency and that physiologic testing (nocturnal frequent sampling) is preferable to pharmacologic testing. The data also reaffirm the impressions of many that even with both tests erroneous diagnoses are still frequently possible.

Siegel SF, Becker DJ, Lee PA, et al: *AJDC* 1984;138:540.

Editor's comment—These data further emphasize how difficult it may be to diagnose all patients with GH deficiency, and therefore how difficult it is to determine precisely the incidence of GH deficiency.

The Effect of Small But Sustained Elevations in Circulating Growth Hormone on Fuel Metabolism in GH Deficiency

This study was designed to examine the effects of maintaining modest but constant levels of circulating growth hormone (GH). To test the hypothesis that some of the metabolic consequences of acromegaly might be attributable to the loss of the normal pulsatile pattern of GH release, Tamborlane and co-workers examined the effects of continuous subcutaneous infusions of GH (CSIGH) on glucose tolerance and apparent insulin sensitivity.

To eliminate the variability introduced by endogenous GH secretion, eight children and adolescents with GH deficiency and 12 normal controls were tested. An oral glucose tolerance test was performed. A 90-hour subcutaneous infusion of GH (corresponding to 0.05 U/kg/24 h) then was started in the GH-deficient patients. On the morning of the fourth day, a second oral glucose tolerance test was done. The results of the glucose tolerance tests were compared with those in seven nonobese children and adolescents.

CSIGH produced small but sustained elevations in GH concentrations (mean, 5.9 ng/ml with a coefficient of variation [CV] of 21%). The normal controls (no infusion) had a mean of 10.1 ng/ml, but a CV of 105%. CSIGH had no significant effects on fasting plasma glucose or insulin levels, but sharply altered oral glucose tolerance (plasma glucose was 30 to 40 mg/dl above preinfusion values). This occurred despite a virtual doubling of insulin secretion during the test.

Only transient changes in fasting free fatty acid concentrations were found, and no significant changes were noted in the fasting concentrations of alanine or branched-chain amino acids. After CSIGH, somatomedin-C (Sm-C) levels increased sharply in two subjects, but remained virtually unchanged in five.

Tamborlane WV: *Pediatr Res* 1984; 18:212.

Editor's comment—It appears that the intermittent pulsatile signal of GH release is as important for maintaining fuel homeostasis as the intermittent secretion of gonadotropin-releasing hormone for the gonadal axis. The sustained nature of constant GH levels, even at a relatively low concentration, is sufficient to induce marked derangements in oral glucose tolerance and insulin action. In five of seven children, these actions occurred in the absence of elevated Sm-C concentrations. Thus, the actions of GH on intermediary metabolism may be the direct effects of GH. For our colleagues who take care of adult patients, these data suggest that severe metabolic alterations and their long-term consequences may accompany so-called mild acromegaly. Since these moderately elevated concentrations of GH can cause metabolic derangements, it may be that anyone whose GH levels are not suppressed into the unmeasurable range is at risk for the continuing metabolic complications of GH excess.

Meeting Calendar

April 13-18 American Academy of Pediatrics Spring Session. Atlanta, Georgia. Contact: American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, IL 60204

May 7-10 American Pediatric Society, Society for Pediatric Research, and Ambulatory Pediatric Association Annual Meeting. Sheraton Washington Hotel, Washington, DC. Contact: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, NJ 08086

May 22-25 4th International Clinical Genetics Seminar. Endocrine Genetics and the Genetics of Growth. Athens, Greece. Contact: Dr. Christof Vartsocas, 47 Vasilissis Sofiais Avenue, Athens 140, Greece

June 15-18 American Society for Bone and Mineral Research Meeting. Washington, DC. Contact: Shirley Hohl (707) 279-1344

June 16-18 45th Annual Meeting and Scientific Sessions of the American Diabetes Association. Baltimore Convention Center, Baltimore, Maryland. Contact: Carolyn Sciortino, ADA, 2 Park Avenue, New York, NY 10016

June 19-21 67th Annual Meeting of The Endocrine Society. Baltimore Convention Center, Baltimore, Maryland. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814

June 22-25 Second Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology. The Hyatt Regency, Baltimore, MD

Address for Correspondence

Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

Pseudopituitary Dwarfism Due to Resistance to Somatomedin: A New Syndrome

Bierich et al report a patient with elevated circulating growth hormone (GH) and somatomedin-C (Sm-C) concentrations. Although birth length and weight were normal (48 cm and 3 kg), all parameters of growth fell behind quickly. At 12 months of age, the infant's length was 58 cm and the weight 5.6 kg. The bone age was 6 months. Dental eruption occurred at 13 months. Hypoglycemia occurred during the second year. Circulating concentrations of Sm-C were increased for age when measured by bioassay at 10 months (1.99 and 2.03 U/ml). Sm-C by specific radioimmunoassay was elevated for age (1.28 U/ml). Administration of 4 IU of GH daily for four days did not increase the levels.

Fibroblasts from a skin biopsy taken when the patient was 21 months old were incubated with ^{125}I Sm-C. Compared with multiple controls, binding to the patient's fibroblasts was diminished by 50%. The authors attribute the abnormality to defective Sm-C receptors.

This syndrome differs from Laron type dwarfism and the dwarfism described by Hayek et al (*J Peds* 1981;99:868) and Kowarski et al (*JCE&M* 1978;47:461). Sm-C concentrations are low in patients with Laron type dwarfism and do not increase after human growth hormone (hGH) administration. Sm-C levels were low in the patients described by Hayek et al and Kowarski et al, but they did respond to GH injections with increased Sm-C levels. In the patient currently presented, the Sm-C concentration was elevated. The authors term all of these types of dwarfism pseudopituitary dwarfism.

Two different actions of Sm-C are discussed. First are the acute effects upon skeletal muscle, heart muscle, and adipocytes. The second are the long-term metabolic effects that act through fibroblasts and chondrocytes. The authors believe that Sm-C works through the insulin receptors and affects the classic insulin-dependent tissues in the acute processes. The long-term or later effects influence fibroblasts and chondrocytes, which are induced to proliferate. In the long term, Sm-C is postulated to act primarily through the specific IGF-I receptors.

Bierich JR, Moeller H, Panke MB, et al: *Eur J Pediatr* 1984;142:186

Editor's comment—This new syndrome is another in the ever increasing list of syndromes in which the patients have GH-deficient–like phenotypes. It is probably one of the least common of such syndromes but it obviously exists. The authors refer in their bibliography to other patients who may have the same syndrome. We have observed one patient at the University of Virginia who unequivocally has this syndrome. We prefer to use the term "short stature with GH-deficient–like phenotype" for all of these patients who do not have GH deficiency.

Robert M. Blizzard, M.D.
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Permit #391

GROWTH
Genetics & Hormones

Vol. 1 No. 2 June 1985

Nutrition, Growth, and Growth Failure

Nutritional causes of short stature and/or poor growth often remain unrecognized by pediatricians and pediatric endocrinologists even though the need for adequate weight gain and body fat to sustain growth during puberty is well described. Although undernutrition resulting from the unavailability of food or psychosocial deprivation accounts for most cases of growth retardation throughout the world, it is a rare cause of short stature in the United States.

When a nutritional deficiency is suspected as a possible cause of short stature, the physician should first ascertain whether the deficit is due to decreased intake resulting from increased energy metabolism, or to increased caloric loss of protein or fat via the stool. A dietary history and/or a brief period of observation in a hospital usually reveals whether there is a decreased intake of calories and/or substrates, hyperactivity, or abnormalities of the gastrointestinal (GI) tract. Anorexia, which can occur as a nonspecific phenomenon secondary to disease or as a primary psychological disorder, is a classic example of poor intake. Nonspecific causes of anorexia—iron deficiency, for example—are seen during infancy and childhood.

Iron deficiency is the end result of an imbalance between the sum of the patient's iron endowment, intake, and absorption, and the sum of his iron needs for growth and replacement of losses. The peak incidence of iron deficiency in childhood is between 6 months and 1 year of age; another such peak is seen during early adolescence. The average American diet provides only 15 to 18 mg of iron per day, of which only an average of 10% is absorbed. The normal daily requirement of elemental iron is 15 mg for an adolescent. It is therefore not surprising that as many as 10% of children have been found to have iron-deficiency anemia. Iron deficiency can also account for anorexia in some high school students.

In addition to looking for evidence of anemia, physicians should also determine serum iron levels, total iron binding capacity, and ferritin levels in infants with failure to thrive and in older children with anorexia. If iron deficiency is found, one should try to determine whether it is the initiating cause of the anorexia or the result. Iron replacement over a period of two to three months may improve growth and appetite regardless of the etiology of the iron deficiency.

Gluten sensitivity (celiac disease) is also associated with low caloric intake and may be associated with

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Problems in Assessing the Efficacy of Growth-Promoting Substances: The Role of Height Prediction

There are two objectives in treating children with growth-promoting substances such as growth hormone (GH) or anabolic steroids. The primary objective is to promote an increase in the child's ultimate height so that he will be taller than he otherwise would have been. The secondary objective is to accelerate the rate of growth, and thus permit the child to achieve an adult height sooner, even if the ultimate height remains unchanged. To attain the second objective, the child must grow at an increased rate over a sustained period, but the increased rate must not diminish the ultimate adult height.

Growth hormone made by recombinant DNA techniques will soon be available, and the opportunity—or temptation—to use it on children who are short, but not GH deficient (GHD), will present itself. The problem is to know whether trials assessing GH in children have been successful and whether there is evidence, at the end of a single year, that GH administration is likely to achieve one or both of the aforementioned objectives.

The first difficulty with these questions relates to the compensatory deceleration of growth observed in GHD patients who are taken off GH therapy. In the year after the first year of therapy, the growth rate is

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anemia as well. Onset most often occurs during infancy. In Europe, much attention has been given to the association between celiac disease without significant GI symptoms and short stature. It is therefore reasonable to suspect celiac disease in children who are short without an adequate explanation. After the child has been challenged with a high-gluten diet for four to six weeks, an intestinal biopsy to confirm the diagnosis of celiac disease can be considered (see page 10 of this issue).

Adolescent girls with ***anorexia nervosa*** of the characteristic type are well recognized by most pediatricians and pediatric endocrinologists. The associated endocrine abnormalities found in these patients are related primarily to undernutrition and are similar to those seen in people with severe caloric deficiency in third world countries. Gonadotropins and somatomedin-C determinations are usually low. Growth hormone levels are usually normal. Since Crohn's disease can masquerade as anorexia nervosa, it should be considered in the differential diagnosis.

Similar to, but certainly not identical with, typical anorexia nervosa is ***"fear of obesity,"*** so termed because it leads to self-imposed malnutrition (see page 9 of this issue). Numerous lay and scientific journals have published articles describing poor growth and delayed development in adolescents who have severely restricted their food intake or gone on fad diets. We recently recognized a group of 14 patients who failed to grow because of self-imposed malnutrition that was rooted in a fear of becoming obese. Their diets were deficient in calories, minerals, and vitamin D. After at least one year of inadequate weight gain, these patients showed signs of deteriorating linear growth and failed to attain puberty, the latter a characteristic also of anorexia nervosa. No organic causes were identified. Once the fear of obesity was recognized, the patients were given nutritional and psychological counseling. They resumed an adequate caloric intake for their age and recovered, as demonstrated by improved linear growth and progression of adolescent sexual development. Only one patient had a permanent alteration of height potential, probably because of delayed diagnosis and treatment. Menarche occurred in this patient soon after adequate weight gain had been established, but her height increased only minimally.

These patients appear to differ from those with other bariphobic syndromes. They had not lost significant amounts of weight, but rather had ceased to gain weight as they progressed along previously defined height percentiles. They also did not have a distorted body image; they realized they were slim and wanted to stay that way. In contrast, patients with true anorexia nervosa lose weight rapidly over a short period and usually see themselves as heavy even though they are markedly undernourished

Unlike classic anorectics, these patients fearing obesity had no self-induced vomiting, did not abuse laxatives or diuretics, did not exercise compulsively, and did not hoard food. We believe that fear of obesity as manifested in these patients represents an exaggeration of our social concerns with achieving and maintaining an "ideal" trim figure. The incidence of this syndrome is unknown, especially since patients with mild forms of the disorder may not even attract medical attention. Interestingly, we have recently identified infants with failure to thrive because of inadequate nutrition (calories were inappropriately withheld) stemming from parental concern about obesity in their children.

Chronic inflammatory bowel disease (CIBD) is another condition that retards linear growth. Growth failure and sexual infantilism (prevalence 30% to 85%) are major complaints in many adolescents with CIBD. Children, however, may be asymptomatic and present primarily for short stature and delayed development. Digital clubbing, aphthous stomatitis, arthritis, or pyoderma gangrenosum are clues to the underlying GI pathology in short-statured patients with CIBD. Growth may slow down or cease without any other sign or symptom, sometimes for more than three years before GI complaints appear. Therefore, CIBD should be considered as a cause of inadequate growth even in the absence of GI complaints Gut motility studies are helpful in confirming the diagnosis, as is an abnormal sedimentation rate, although not all patients with CIBD have abnormal rates.

Children with ***Crohn's disease*** or ***ulcerative colitis*** may not grow normally because of impaired nutrient absorption, decreased nutrient intake, specific nutrient deficiencies, or increased protein losses through the GI tract. Glucocorticoid excess during treatment with steroids is another cause. While some children with CIBD have intestinal malabsorption, the majority do not have significant steatorrhea and are able to absorb xylose normally Thus, malabsorption of nutrients does not fully explain the poor growth in most of these patients. Anorexia, however, plays a significant role in patients who have abdominal pain following meals and who may also be losing protein through the GI tract.

Nutritional rehabilitation often promotes growth in growth-retarded children with CIBD. Short-term parenteral nutrition in a hospital, as well as long-term total parenteral nutrition at home, can produce marked increases in height and catch-up growth. Oral feedings may also promote catch-up growth if enough nutrients are ingested. On occasion, nutritional rehabilitation has induced remission of the disease, suggesting that adequate nutrition is needed to control it. Appropriate nutrition may also be necessary for medications such as sulfasalazine or steroids to exert their therapeutic effects, which in turn may permit the resumption of normal growth.

Zinc metabolism and deficiency are associated with a number of clinical syndromes. Moreover, many recent articles have implicated zinc deficiency as a cause of growth retardation.

Zinc is an essential nutrient. Adolescents and adults require 15

mg/d; infants and children require 3 to 5 mg/d in their first year and 10 mg/d until early adolescence. Zinc deficiency may result from malabsorption states, or it may develop during total parenteral nutrition or along with cirrhosis of the liver and renal disease. Symptoms of mild to moderate zinc deficiency include diminished taste sensitivity, anorexia, and growth retardation. Acrodermatitis enteropathica, diminished cellular immunity, and poor wound healing may also indicate zinc deficiency. High concentrations of dietary phytate (as seen in the typical Iranian or Egyptian diet) can diminish the availability of zinc and precipitate zinc deficiency syndromes. The clinical diagnosis of zinc deficiency can be confirmed by a low concentration of *plasma* zinc. Zinc levels in hair are unreliable indicators of deficiency.

In summary, physicians must recognize the important role that nutrition plays in normal and abnormal growth. Indeed, nutritional causes of growth disturbances may be as obscure and subtle as endocrine causes such as partial growth hormone or thyroid deficiency.

Fima Lifshitz, M.D.

References will be supplied upon request to Dr. Blizzard.

Address for Correspondence

Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

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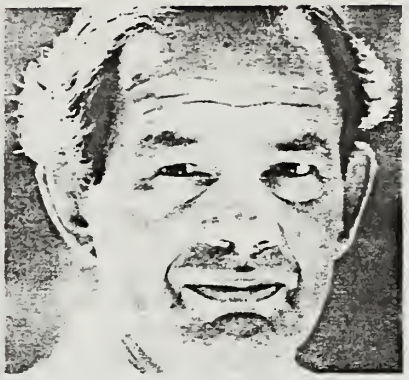

Jürgen R. Bierich, M.D.

A native of Hamburg, West Germany, Dr. Bierich has been Professor and Chairman of Pediatrics at the University of Tübingen since 1968. After graduating from the Medical School of Hamburg University in 1946, he served his residency in pediatrics under Drs. Degkwitz, Eckstein, and Schäfer in Hamburg. He also served a residency in internal medicine under Dr. Jores in the same city.

During his residencies and for several years thereafter, Dr. Bierich's major scientific interest was pediatric endocrinology. Much of his work dealt with the physiology and pathology of the pituitary and adrenal glands, as well as with sexual maturation.

Dr. Bierich received the title Privat-Dozent in 1956 and was appointed Professor in 1962. During 1963 and 1964, he served as President of the European Pediatric Endocrinology Club, which was later renamed the European Society of Pediatric Endocrinology. A decade later, in 1973 and 1974, he served as President of the German Society of Endocrinology. In 1979, he was elected to membership in the German Academy of Natural Scientists Leopoldina.

An author or coauthor of numerous articles, Dr. Bierich is currently involved in work concerning problems of growth and development and pediatric aid in the third world.

Associate Editor:

David L. Rimoin, M.D., Ph.D.

Born in Montreal, Quebec, Canada, Dr. Rimoin has lived in California since 1970, when he joined the staff of Harbor-UCLA Medical Center in Torrance as Chief of the Division of Medical Genetics. He has also been Professor of Pediatrics and Medicine at UCLA School of Medicine since 1973. In addition, he is a consultant physician to several hospitals in the Los Angeles area, including Cedars-Sinai Medical Center, Orthopedic Hospital, and Shriners' Hospital for Crippled Children.

Dr. Rimoin graduated from McGill University in Montreal (with first class honors in genetics) in 1957. He received both his medical degree and a Master of Science degree in genetics from McGill University in 1961. He then served a rotating internship at Royal Victoria Hospital and Montreal Children's Hospital, and a residency in medicine at Royal Victoria. He continued his residency in medicine at Johns Hopkins Hospital in Baltimore. Between 1964 and 1967, he was a Fellow in Medicine (medical genetics) at The Johns Hopkins University School of Medicine. He received his doctorate in human genetics from that institution in 1967.

Between 1979 and 1983, Dr. Rimoin was President of the American Board of Genetics. In 1984, he was President of the American Society of Human Genetics. As author of more than 200 articles, 8 textbooks, 17 chapters in books and atlases of genetic defects, and 141 abstracts, Dr. Rimoin has written extensively on genetics, diabetes, endocrine disorders, and growth disorders.

Problems in Assessing the Efficacy of Growth-Promoting Substances: The Role of Height Prediction

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even slower than the rate before treatment. In 14 prepubescent patients whom we studied, growth velocity was 3.4 cm/yr before treatment, 8.1 cm/yr during treatment, and 2.2 cm/yr posttreatment. In addition, 13 children with the Silver-Russell syndrome had growth velocities of 5.4 cm/yr, 6.8 cm/yr, and 4.6 cm/yr in their pretreatment, treatment, and posttreatment years, respectively. The deceleration was greater in the first six months of the posttreatment year than in the second six months in both groups of patients.

Some slowing of the growth rate in the posttreatment years, compared with the pretreatment year, is expected, since growth velocity normally declines during prepubescent years. Corrections can be made for this slowing by using the standard velocity curves of Tanner, Whitehouse, and Takaishi. The estimated net gain during the year of treatment is given by a formula:

$$V_T + V_2 - 2(V_1 - D_T) + D_2$$

V represents velocity, D_T, the expected normal diminution of velocity from pretreatment to treatment year, and D_2, the normal diminution from treatment to posttreatment year. As calculated by this method, the net gain in the Silver-Russell children was only 0.5 cm/yr. Some heterogeneity of response is concealed, however, as two of the 13 children had net gains of over 3 cm, and the remaining 11 had no indication of any net gain.

Such compensatory deceleration may be irrelevant with continuous treatment over many years, but this is difficult to judge without a clinical trial that continues for the entire period of observation. In considering the results of a one-year trial, one must take the posttreatment year into account.

There is difficulty also in evaluating short-term *v* long-term effects of GH treatment. Nitrogen balance studies, which were used when treatment with GH was a new therapy, demonstrated that there was little correlation between short-term nitrogen retention and long-term growth response in GHD patients. This was not surprising since short-term response can only predict long-term response if all patients have similar time courses of response to treatment.

Worse still, there is considerable doubt whether even the response in height velocity during the entire first year is predictive of the final outcome. In treated GHD patients, the strongest correlation of final adult height is with parental height, just as in children of normal stature. So, in examining the relation between first-year velocity and final height, parental height must be taken into account, either by using partial correlations or by considering final height as standard deviations (SD's) of the parental height target.

Burns et al found a correlation of only 0.22 between first-year velocity and final height in 39 idiopathic GHD patients treated until growth ceased. Joss et al found a correlation of 0.65 between final height and the *increase* in velocity in 18 GHD patients. Since Joss et al found no relation between pretreatment velocity and final height, the coefficient of 0.65 is derived largely from the first-year velocity; this is in contrast to the findings of Burns et al. All that can safely be said at present is that the first-year response is certainly *not* a good guide to the final result, and may be no guide at all.

Short-term testing of bone growth response to treatment over periods of one to three months was recently proposed, but it is probably not relevant when assessing whether objectives are achieved. Even the observation of growth velocity or acceleration in the first year of treatment may be of limited value in relation to our prime objective.

There may be a third difficulty: the effect of the psychophysiologic changes accompanying the increased attention paid to subjects—the famous "Hawthorn effect." Although there are no solid data at present, every clinician dealing with growth disorders knows how sensitive the patient's growth rate is to subtle differences in psychosocial factors. Occasionally, we have seen an increase in growth rate during the year *before* treatment begins, a year filled with tests, measurements, and anticipation.

Thus, any trial assessing a growth-promoting agent should include a placebo. In a current trial of GH in short-statured non-GHD children, we have had no difficulty in securing parents' agreement to a double-blind design in which an inert substance would be injected for

Table Increment in Prediction During Treatment (cm)

	1st Year	2nd Year	3rd Year	First 2 years	First 3 years
Growth hormone deficient					
Males (51)					
Mean	5.2	2.7	2.1	7.9	10.0
Range	1 to 12	-1 to 9	-2 to 9	2 to 21	3 to 24
Females (15)					
Mean	4.1	2.0	0.0	6.1	6.1
Range	1 to 9	-1 to 7	-5 to 3	0 to 15	1 to 18
Small/delay					
Males (19)					
Mean	-0.3	0.2		0.0	
Range	-2 to 2	-3 to 4		-5 to 6	
Silver-Russell (11)					
Mean	2.2				
Range	1 to 4				

six of the 12 months. Parents were assured that treatment would continue if the comparison showed a significant effect of GH in their own children.

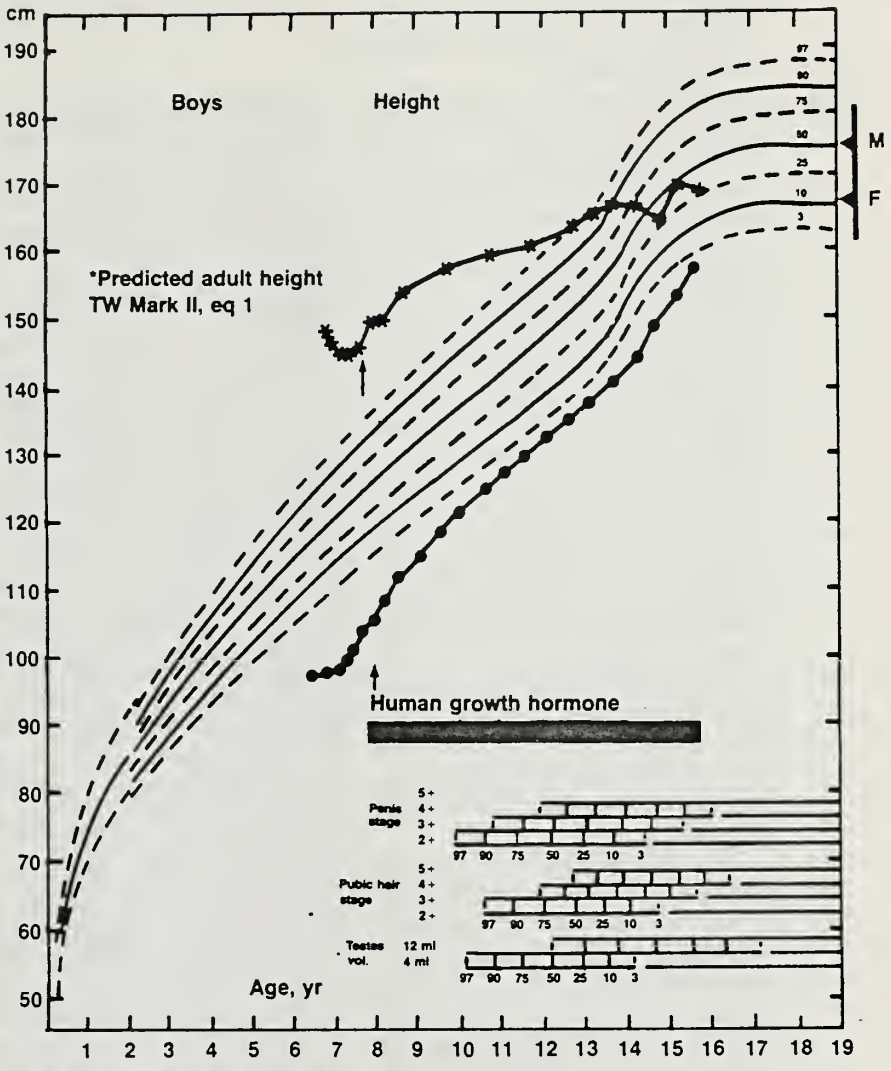
Height Prediction

Having discussed the difficulties, we can turn to a possible method of assessing the effect of growth-promoting agents. A change in the prediction of adult height while the patient is receiving treatment could be a very positive indicator, although such predictions need to be evaluated with caution.

Predicted adult heights for children with idiopathic GHD whose treatment begins between ages 5 and 11 are, according to the Tanner Whitehouse (TW) system of equations, an average of 150 cm in males (4 SD below the mean) and 145 cm in females. This probably represents, at least approximately, the height these children would have attained without treatment. Some might say that this is an overestimation since Rimoin et al have reported that males and females with hereditary-isolated GHD averaged 132 and 128 cm, respectively.

However, the majority of GHD patients are less severely affected than those with hereditary GHD. When GH is given, the prediction rises, reflecting the greater advance in height velocity than increase in bone age. Probably this increase in prediction is the best indication, at present, of whether we are achieving an increase in final adult height when we give a growth-stimulating agent.

It seems that this increase does not take place in GHD patients if Bayley-Pinneau predictions are used. These are too inflexible to allow for the significant retardation in bone age, and the predictions made at the beginning of treatment are excessive. The same applies to boys with constitutional delay of growth. It is unknown whether the prediction equations of Roche and co-workers (based on bone-specific Gruelich-Pyle ratings of the hand and wrist or knee) would show the increase with treatment; like the TW system, these equations are based on regression equations, and there seems no reason why they should not behave in the same way.



Increments of Predicted Adult Height

My colleagues and I recently studied the change in prediction in three groups of subjects. The predictions were made using the TW RUS Mark II system, equation 1. We used the records of all current patients with idiopathic GHD, who had been treated for three years or more starting before age 11. There were 43 males and 15 females. Eight males whose treatment had been completed were added. Puberty had not developed during the first three years of treatment. The average ages at the beginning of treatment were 7.4 and 7.6 years in boys and girls, respectively, with ranges of 4.6 to 10.9 and 4.7 to 10.4. The respective mean SD scores (SDS) of height for chronological age at the beginning of treatment were -3.9 and -4.0. Those patients who had thyroid-stimulating hormone and cortisol deficiency were given thyroxine and cortisol as necessary.

Treatment with GH was either 10 U/biw, 5 U/biw, or 4 U/biw. The Table shows the increments of predicted height obtained in the first, second, and third years of treatment. The Figure shows a typical example. In the first year, the prediction rose on an average of 5.2 cm in boys and 4.1 cm in girls. The increment in the second year was approximately half as much as in the first, and in the third year it diminished further. Over the first two years combined, the prediction rose by 7.9 ± 0.5 cm, and over the first three years it rose 10.0 ± 0.7 cm. The ranges, however, are considerable: from 1 to 12 cm in the first year, 2 to 21 cm in the second year, and collectively, 3 to 24 cm in the first two years.

As one might expect, there was some tendency for patients with the lowest initial SDS for height to improve their predictions most, but the tendency was not strong (r = -0.3). In eight of these boys whose final

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Problems in Assessing the Efficacy of Growth-Promoting Substances: The Role of Height Prediction

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heights are available, the difference between their initially predicted adult heights and their actual attained heights averaged 16 cm, with a range of 5 to 26 cm. An additional five mature boys, whose treatment started between ages 11 and 13, gained the same amount over the initial prediction. Those starting treatment later than age 13 gained less. There was no difference between the groups that had isolated GHD and GH plus other growth-related hormone deficiencies. Ten of the boys with multiple deficiencies, who were treated with testosterone at the pubertal age and who had reached their final height, gained an average of 18 cm over the initial prediction.

A small number of patients with GHD due to craniopharyngiomas and other anatomic lesions were studied. They appeared to increase their predictions less than patients with isolated GHD.

The second group of patients consisted of 19 males who were followed for growth delay and seen before age 11. Their average age at first examination was 7.3 years (range, 4.1 to 10.5) and their average SDS of height for chronological age was −2.6. The results for these patients are included in the Table. No treatment was given. The mean change in prediction was almost exactly zero. The range in the first year was small, −2 to +2 cm.

The third group consisted of 11 patients of both sexes with Silver-Russell syndrome. GH treatment with 10 U/biw was begun before age 11 (average age was 6.4 years, with a range of 3.9 to 9.3). Their average SDS of height for chronological age was −3.9. In age and SDS they were thus comparable to the GHD patients. The results for the Silver-Russell patients fell between those of the other two groups. Data from only one year of treatment were available. In this year, there was an average increment in prediction of 2.2 ± 0.4 cm. The range was 0 to 4 cm.

The increments of prediction in the GHD patients we evaluated fall between those reported by Ranke et al and by Joss et al. Ranke used TW RUS Mark I, CABA-(chronological age–bone age) based equations. He obtained a mean prediction increment of about 6.5 cm during an average of four years of treatment. Vicens-Calvet et al, using the same equations, obtained a 7.2-cm increment over three years in four children receiving 12 U/wk of GH and 13.0 cm increment in five children on 24 U/wk over three years.

Joss obtained an increment of 10 cm in the first year alone and a further increase of 10 cm in the subsequent three years. His patients were older, with an average age of about 12.0. In addition, he used the TW RUS Mark I system of equations based on bone age alone, a system originally intended for use only on certain occasions when the CABA system was not applicable. His beginning-of-treatment figures, however, indicate that he would have obtained lower increments if the CABA system had been used.

With continuous treatment, the predicted height gradually approaches the height actually to be attained in GHD patients. But looking at individual long-term records reveals that in middle or late puberty, the predictions usually seem to be too high by an average of about 4 cm (range 2 to 7 cm). This may be due to a defect in the predictions when applied to this time period. Use of Mark II, equation 3, which allows for height velocity in the previous year, reduces this excessive prediction to an average value of 2 cm. However, the excessive prediction may also mean that the treatment during puberty is less than optimal. It now seems clear that the total 24-hour secretion rate of GH may increase during puberty, so perhaps we should be giving a greater amount of human growth hormone (hGH) at that time. If we did so, we might obtain an extra 2 to 4 cm in response.

In the early days of hGH treatment, we employed a protocol of one pretreatment year, followed by one treatment year, followed by one posttreatment year. This was followed by continuous treatment, if justified. We have observed 12 patients during this posttreatment year. As expected, the predictions dropped, on average, during this year. The mean drop was 2 cm (with ten of the 12 decreasing between 0 and 3 cm). In all other respects, these 12 patients resembled those discussed above.

In summary, difficulties in assessing the efficacy of hGH or other growth-promoting substances related to (a) compensatory deceleration, (b) short-term *v* long-term effects, and (c) placebo effects. Change in the adult height prediction during treatment offers a possibility for testing the outcome of treatment with growth-promoting agents. In 66 idiopathic GHD patients whose treatment started before the age of 11.0, the prediction rose by an average of 5 cm in the first treatment year, 8 cm in the first two years, 10 cm in the first three years, and 16 cm (in eight subjects only) in all the years until growth ceased. In 19 patients with growth delay who were not treated, no average change of prediction occurred over a control year, and in 11 Silver-Russell syndrome patients there was an average increase over the first year of treatment of 2.2 ± 0.4 cm.

The difficulty in evaluating the effect of a growth-promoting agent is evident from the discussion of the data presented. Continuous GH therapy in patients with GHD undoubtedly permits both of the treatment goals to be achieved in most instances. However, to ascertain whether either or both of the goals necessary to evaluate the value of a growth-promoting agent are met, it is quite evident that many studies need to be done in patients with short stature that is not associated with GHD.

References will be sent on request to Dr. Robert Blizzard.

James M. Tanner, M.D.
Professor of Child Health and Growth
University of London Institute of Child Health
London, England

Dr. Tanner is a guest contributor for this issue. He is a world-renowned authority on growth, development, and anthropometrics.

Malnutrition: Definition, Incidence, and Effect on Growth

With reports from famine-stricken regions appearing almost daily on radio and television, any discussion of energy-protein malnutrition (EPM), its definition, its incidence, and how it affects growth, is particularly timely. An estimated 200 million to 1 billion people in the world suffer from EPM. However, EPM is an ambiguous concept, and it is therefore difficult to determine what, if anything, these prevalence estimates mean.

The basic problem in understanding EPM is that it is defined by three different criteria: (1) *dietary deficiency*, where the intake and/or utilization of energy and protein nutrients are lower than the recommended daily allowances; (2) *substandard anthropometry*, where a person is below the international or local measurement standards of height and weight for age, weight for height, or skinfold thickness; and (3) *functional impairments*, where dietary deficiency results in physical, mental, or emotional changes. High rates of morbidity are linked to functional impairment through decreased immunocompetence, impaired efficiency of physical work performance, impaired mental performance, and emotional stress caused by sensations of hunger.

By utilizing a Venn diagram (Figure), one can identify seven sets of EPM. Dietary deficiency, substandard anthropometry, or functional impairment can occur alone (set 1, 3, or 7) or in various combinations (set 2, 4, 5, or 6). A closer look at these sets reveals the imprecise nature of the definitions given for the three major categories. Many people in set 7 may have functional impairments from disease, emotional stress, social or environmental deprivation, exposure, or other dysfunctional factors of poverty rather than from dietary deficiency. Also of great interest are individuals in set 3: They may have substandard anthropometry of genetic origin and not be functionally impaired. Heredity may be the etiology for the majority of people with substandard anthropometry, who are nevertheless considered to suffer from EPM by the present definitions. If these energy-protein standards and statistical procedures used to estimate dietary deficiency in developing countries were applied to the United States, 67% of males and 80% of females would be considered EPM victims. Do we seriously believe that such a large proportion of the US population is undernourished?

Reexamining the diagram, one sees that only those individuals who fall in set 5 have malnutrition characterized by diminished intake, substandard anthropometry, *and* functional impairment. This set represents a smaller number of EPM victims than would be identified when a broader definition of EPM—for instance, only one of the three standards—is applied.

To reduce the confusion surrounding the definitions of malnutrition, one must consider two alternative theories of the growth process and be acquainted with the "small-but-healthy" hypothesis.

The average person usually thinks of malnutrition in terms of thin, wasted people who have substandard weights for height—in other words, acute EPM. Chronic EPM occurs often when the individual is below standard height-for-age levels. While it may be thought that most people with chronic EPM also have acute EPM, this is not necessarily true. In a study that assessed the nutritional status of children aged 6 to 18 months in 14 developing countries, it was found, on the average, that 90% of the EPM encountered was chronic rather than acute. These children had low height for age, but normal weight for their short stature. Further, only 17% of those with low weight for age had low weight for height according to the classification system used (Gomez). The children who are short but have normal weight typify the small-but-healthy hypothesis. Even though they are not underweight for height, and are thus likely to be considered healthy, they may be nutritionally dwarfed.

Most published reports assume these children are not healthy, but without independent evidence of functional impairment, the meaning of this kind of malnutrition is ambiguous. If, on the other hand, these children are healthy, one must wonder why they are short even though they have appropriate weight for height and other body proportions, body fat, and satisfactory general health. According to the small-but-healthy hypothesis, these children are healthy, but their small size is often the result of decreased caloric and/or protein intake.

Of the two theories of human growth, the *deprivation theory* is the predominant one. It is assumed that every individual is born with a single, genetically determined growth po-

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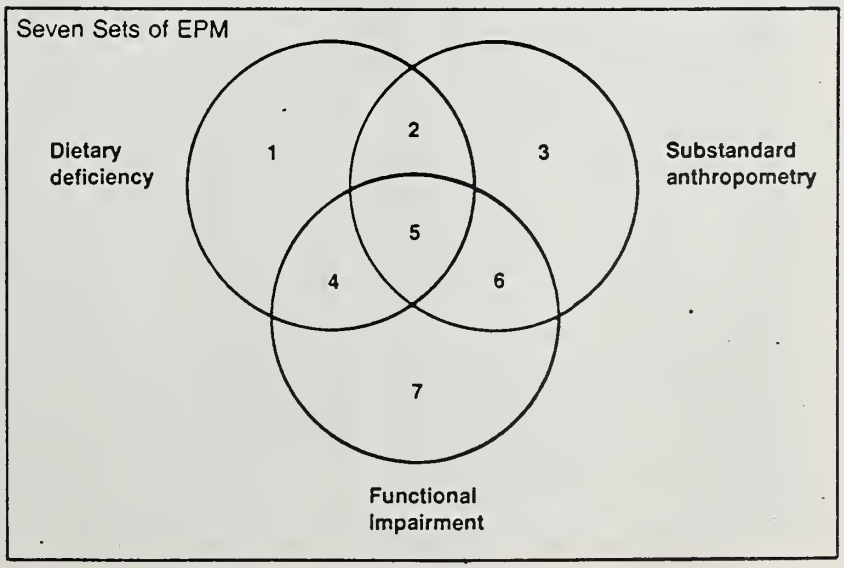

Malnutrition: Definition, Incidence, and Effect on Growth

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tential. It is further assumed that a healthy and well-nourished child will grow to his or her genetic potential. In contrast, by definition, growth that is significantly below genetic potential indicates functional impairment. Of course, some individuals are normally small, but this may be difficult to determine. Nevertheless, in large populations, a skew of the distribution curve of height toward lower stature is perceived as functional impairment within that population.

In contrast to this view, the *homeostatic theory* of growth holds that the genetic endowment of the organism interacts with the environment in a system of cybernetic control to maintain homeostasis. According to this theory, the genetic growth potential of the deprivation theory is replaced by a broad array of potential growth curves in several anthropometric dimensions—a potential growth space, in other words. Within the bounds of this potential growth space, the growing organism may be mapped through various paths of size and shape in response to nutrition, disease, climate, activity, emotional stress, and other environmental influences.

The homeostatic theory promulgates that a major control instrument is the regulation of growth rate with respect to the height of the child. If, for example, nutrient constraints are encountered at a given rate of growth, the rate is slowed to bring nutrient demand into equilibrium with supply. Similarly, the growth rate may be accelerated in response to overconsumption. According to this theory, neither nutrient constraint nor overconsumption is necessarily abnormal; they are merely adaptations. Through regulation of the speed of internal physiologic "clocks," short-term equilibrium can be established and the ultimate size and shape of the adult molded to the environment. Of course, there are bounds to these adaptive possibilities. If deprivation is severe, acute EPM may be superimposed on the expected short stature that may result from a modest decrement in caloric intake or utilization.

Thus, while the deprivation theory postulates a continuous relationship between small size and the functional impairments of EPM, with the incidence and severity of deficiencies increasing as the size of the organism decreases, the homeostatic theory essentially postulates a discontinuous, threshold relationship. According to the latter theory, smallness is not necessarily correlated with functional impairment, although there is a high incidence and severity of functional impairment as the lower boundaries of size are transgressed. Thus, children with mild to moderate chronic EPM are likely to remain small but healthy. With regard to acute EPM and moderate to severe chronic EPM, the two theories are concordant.

If the homeostatic theory is valid, it explains why many small persons are not functionally impaired. In a study of Bangladeshi children, Chen et al found a high incidence of mortality in those with severe EPM, but no difference in mortality between children with mild to moderate EPM and normal children. Once some difficult statistical problems due to aggregation of individual variation in thresholds are better sorted out, similar threshold effects are likely to become apparent.

In summary, the essential difference between the deprivation and homeostatic theories is the difference between maximum and optimum. The deprivation theory states that the optimal size must be in accord with the maximum genetic potential. Hence, it follows that smallness is bad per se. The homeostatic theory, on the other hand, defines optimal size in terms of a functionally stable growth space that may be considerably below maximum height-for-age ratios. The lower boundary of the growth space, where significant functional impairments begin to occur, can be determined only by empirical research. Thus, while the deprivation theory deduces functional impairment from the premise that maximum growth is necessary to health, the homeostatic theory requires evidence of functional impairment to define EPM. To date, the incidence of malnutrition has been defined primarily in relation to the deprivation theory.

The differences between the deprivation and homeostatic theories open important fields of research in pediatrics, genetics, endocrinology, and even economics. If it is found that the growth, and perhaps the shape, of the human body are controlled by factors other than nutrition and disease—genetic and environmental interactions, for example—then pinpointing the control mechanism and what it responds to becomes of great scientific interest.

In terms of nutritional policy, it seems clear that nutritional resources now being devoted to accelerating the linear growth of children should be reallocated to those children in clear and present danger of functional EPM: namely, those with serious to severe acute EPM (underweight for height). This approach would reduce the target population of nutritional programs to less than 10% of the children who are conventionally defined as having EPM. With proper management, the resources now largely being spent on accelerating linear growth in small but relatively healthy children could eradicate functional EPM. In fact, attempts to get children on higher growth curves before their poverty has been alleviated may put them out of equilibrium with their environment and do irreparable harm.

References will be supplied upon request to Dr. Blizzard.

David Seckler, Ph.D.
Professor of Agricultural and Resource Economics
Colorado State University
Fort Collins, Colorado
Senior Development Policy Advisor
United States Agency for International Development (USAID)
Jakarta, Indonesia

Dr. Seckler is a guest contributor for this issue. Before assuming his current posts, he was a Ford Foundation scholar in New Delhi, India, for five years (1978 to 1983). The views expressed here are the author's own and do not necessarily reflect those of USAID.

Studies of Marginal Zinc Deprivation in Rhesus Monkeys: (IV) Growth of Infants in the First Year and (V) Fetal and Infant Skeletal Effects

Growth retardation, delayed skeletal maturation, and defective bone mineralization are reported in rhesus monkeys subjected to marginal zinc deprivation during the prenatal period and throughout the first year of life. The subjects were offspring of mothers given either a zinc-deficient diet (4 mg/kg of zinc) or a control diet (100 mg/kg of zinc) throughout gestation and lactation. At weaning, the offspring were fed either a zinc-deficient or control diet corresponding to the maternal diet. A complete morphometric examination, a quinine acceptance test for taste sensitivity, blood samples for trace metals, and bone x-rays were performed at various intervals during the first year of life.

At birth, zinc-deficient males had significantly lower body weights, crown-rump lengths, and femur lengths than control males. These data suggest intrauterine growth retardation. Reduced rates of weight gain and crown-rump length growth were reported in the zinc-deficient group compared with controls at 9 to 12 months of age. The diminished rate of weight gain was positively correlated with reduced food intake, lower food-use efficiency, and decreased taste acuity at 1 year of age. Overall, zinc-deficient infants did not grow as well as the controls during the entire first year of life.

At birth, zinc-deficient infants demonstrated delayed skeletal maturation without defective mineralization. However, by 1 month of age, abnormal mineralization was reported in the zinc-deficient group. Specifically, there were changes suggesting rachitic syndromes with "frayed" metaphyses and "splayed" cortices.

As a result of these observations, the authors suggest that marginal zinc deficiency during gestation results in neonatal growth retardation that persists throughout the first year of life. Bone maturation delay and defective mineralization of the skeletal system also result from zinc deprivation.

Golub MS, Gershwin ME, Hurley LS, et al: *Am J Clin Nutr* 1984;40:1192; and Leek JC, Vogler JB, Gershwin ME, et al: *Am J Clin Nutr* 1984;40:1203.

Editor's comment—*These observations are important since they demonstrate that marginal zinc deficiency can lead to growth abnormalities in utero and to defective skeletal growth. These abnormalities resulted without inducing hypozincemia, but the mean values of the plasma zinc levels were lower in the zinc-deficient monkeys than in the control animals. Unfortunately, the maternal plasma zinc levels are not reported.*

These data also demonstrate the need for zinc in skeletal mineralization and the regulation of bone formation. Radiographic findings of rickets were associated with zinc-deficient diets. Unfortunately, vitamin D levels were not obtained. The above observations may be important clinically, since decreased intake of dietary zinc is often seen during pregnancy. In childhood, marginal zinc deficiency is often seen in conditions associated with poor growth.

Fear of Obesity: A Cause of Short Stature and Delayed Puberty

Fourteen of 201 children evaluated for short stature and/or delayed puberty over a 25-month period were found to fit a pattern of growth failure due to self-imposed restriction of caloric intake arising from a fear of becoming obese. Nine males and five females, ages 9 to 17 years, underwent a complete evaluation. They were all below the fifth percentile for weight and height. All showed deterioration of linear growth, which was preceded by one to two years of inadequate weight gain. The weight deficit for height was 5% to 23% of ideal body weight.

Seven of the older patients had delayed puberty. Physical examination and routine diagnostic laboratory examinations revealed no evidence of organic disease.

Review of the patients' 24-hour dietary intake by recall indicated that they ingested only 32% to 90% of the recommended caloric intake for age and sex. Nine skipped meals regularly. They tended to reduce the amount of animal proteins in the diet, but consumed increased amounts of cereals, fruits, and vegetables. The seven-day record in nine patients supported the data obtained by recall.

An open-ended interview of all patients revealed no evidence of psychiatric disease or anorexia nervosa. As a group, these patients were good students with compulsively shy personalities. Seven underwent the Diagnostic Interview for Children and Adolescents, which also revealed no psychiatric disease. Three patients did show evidence of an oppositional disorder (usually, argumentative or confrontational behavior).

After receiving nutritional counseling and nonstructured psychiatric counseling, the patients resumed an adequate caloric intake for age. Weight gain and a resumption of linear growth accompanied increased food intake, except in one female who underwent menarche and remained stunted.

Pugliese M, Lifshitz F, Grad G, et al: *N Eng J Med* 1983;309:513-518.

Editor's comment—*This paper describes a newly recognized cause of poor growth in adolescence. It remains to be seen whether fear of obesity, which may be prevalent in our population because of concern over being fat, is a distinct disease entity with its own natural history. This entity could also be a mild variant of anorexia nervosa. Whether a caloric deficiency or the inadequate intake of a specific nutrient caused the poor growth remains unclear.*

Short Stature and Celiac Disease: A Relationship to Consider Even in Patients With No Gastrointestinal Tract Symptoms

Celiac disease (CD) as a frequent cause (8.3%) of short stature in an asymptomatic group of 60 short children is reported by Cacciarri et al of Bologna, Italy. Duodenal biopsies were performed on 60 children (39 boys and 21 girls, 3½ to 18 years of age) who were less than the third percentile, who had no apparent cause for their short stature, and who had no gastrointestinal symptoms. All were tested for human growth hormone (hGH) release using arginine and L-dopa, and for xylose absorption, antireticulin antibodies, hemoglobin, and serum iron. The migration inhibitory factor (MIF) was tested in those with duodenal pathology and in a limited number of the others. Anthropometric measurements and skeletal maturation were assessed in all.

Five children (two girls and three boys) had total villous atrophy. These five did not differ in delay of bone age, height SD score, weight SD score, height age/bone age, or height age/weight age from the 52 patients for whom no cause of short stature was found. Surprisingly, the height age/weight age was 1.03 ± 0.17 SD for the five children, which indicates no malnutrition for the group. Data for individuals are not given.

The data regarding antireticulin antibodies, xylose absorption tests, MIF tests, hemoglobin, and basal iron did not differentiate completely those patients with villous atrophy. For example, only three of five patients had abnormal xylose tests and antireticulin antibodies. Only two had positive MIF tests, decreased basal iron levels, or a history of frequent diarrhea during infancy. The article does not clarify whether the same patients had the same laboratory abnormalities. All five did have delayed bone age.

The authors state that the results do not allow statistical interpretation and absolute conclusions, but they do allow certain conclusions: (1) the incidence of celiac disease may be significant in a population of short children who are asymptomatic; (2) at present, the only way to produce a definite diagnosis in all children with celiac disease is to perform intestinal biopsy; (3) if biopsies are done only in patients with a history of diarrhea in the first two years of life, and/or the presence of antireticulin antibodies, and/or an abnormal xylose test, the number of biopsies that need be done for diagnostic purposes is significantly reduced. Four of the five would have been identified by the presence of at least one of these three factors, and only 22 biopsies would have been done in the 60 patients; and (4) growth hormone (GH) secretion is normal in these patients with celiac disease.

Cacciarri E, Salardi S, Lazzari R, et al: *J Peds* 1983;103:708.

Editor's comment—*The data are intriguing. This is not the first report, as the authors readily state, of diagnosing celiac disease in children with short stature and without symptoms of gastrointestinal disease. Groll et al reported that eight of 34 children with short stature and without gastrointestinal disease had intestinal biopsies characteristic of CD, and seven grew significantly on a gluten-free diet (*Lancet *1980; 1:1097).*

A little disturbing is the absence of repeat biopsies in either study to demonstrate alterations of histology toward normal. This would have been particularly helpful in the current study, as three of these patients had some adolescent changes during the observation period. Thus, one may not be able to exclude attributing the changes in height and weight to adolescent development.

In the United States and Canada, celiac disease is reported to occur less frequently than in Europe. It is therefore possible that we are missing asymptomatic cases. Letters to the editor concerning this topic are invited.

Bone Marrow Transplantation in the Maroteaux-Lamy Syndrome (Mucopolysaccharidosis VI)

The authors report the use of bone marrow transplantation as treatment for the severe form of Maroteaux-Lamy syndrome in a 13-year-old girl who continues to show improved biochemical and clinical status 24 months after transplantation.

Bone marrow transplantation is now the treatment of choice for many leukemias, aplastic anemias, and immunodeficiency disorders. In experienced hands, when using marrow from HLA-MLC–matched sibs, complication rates and survival times have become quite acceptable. The possibility of using bone marrow transplantation for inborn errors of metabolism has been discussed for many years. Recently, bone marrow transplantation has been used, with encouraging results, for one form of osteopetrosis (an inherited disorder with osteoclast dysfunction) to restore the marrow's osteoclast-monocyte population.

Selective enzyme deficiencies such as Maroteaux-Lamy syndrome would appear to be candidates for this type of treatment. Maroteaux-Lamy syndrome, for which there is an animal model, is a lysosomal disorder that spares the CNS. Using the feline mucopolysaccharidosis VI model, bone marrow transplantation experiments demonstrated that transplanted reticuloendothelial and hematopoietic cells could return to almost normal the biochemical and clinical abnormalities present in affected animals.

With this background, a 13-year-old girl with the severe form of Maroteaux-Lamy syndrome was identified for bone marrow transplantation. Her disease had become life-threatening with the development of frequent apnea episodes and severe congestive heart failure. Her sister, who was HLA-DR–identical, was the bone marrow donor. The patient was pretreated with busulfan and a graft-v-host preventive regimen.

Her response to therapy was monitored by clinical response, liver biopsy changes, white cell enzyme assays, urinary mucopolysaccha-

ride output, and electron microscopic (EM) studies of liver cells, bone marrow cells, peripheral blood leukocytes, and platelets. After engraftment, blood-group studies demonstrated the presence of only donor cells.

Peripheral leukocytes, which had been severely deficient in arylsulfatase B prior to bone marrow transplantation, showed normal activity by two months after transplantation and remained normal for the 24-month observation period. Liver biopsies revealed apparent repopulation with Kupffer's cells after bone marrow donation, with the ratio of arylsulfatase B to arylsulfatase A activity increasing from 3% to 16% of normal activity. Accumulation of mucopolysaccharides in hepatic Ito cells decreased so that no storage material was seen 148 days after transplantation. No storage material was seen on EM studies in hepatocytes. Kupffer's cells, or endothelial cells in posttransplantation biopsy specimens. Urinary excretion of mucopolysaccharides decreased and was within normal limits by 100 days after transplantation.

Pulmonary hypertension, cardiomegaly and thickening of ventricular walls, and congestive heart failure had been present prior to transplantation, but resolved completely 15 months after transplantation. Pulmonary function also returned to normal by this time, and apneic episodes ceased. No change in radiologic abnormalities of the bones could be demonstrated, but there was subjective improvement in the range of motion in most joints. Visual acuity improved, but glaucoma and corneal clouding remained unchanged. There was a marked decrease in hepatic mass, and the spleen returned to normal size posttransplant. Intellectual status remained normal, but the general sense of well-being was markedly improved. Now 24 months posttransplant, the patient has shown remarkable improvement in severely affected areas without any evidence of deterioration in new areas.

Krivit W, Pierpont ME, Ayaz K, et al: *N Engl J Med* 1984;311:1606.

Editor's comment—*This report describes an exciting new mode of therapy for some inherited disorders with inborn errors of metabolism. However, it is important to emphasize that this mode of therapy will be appropriate only in selected diseases that involve either bone marrow elements or reticuloendothelial cells which, when transplanted from an unaffected individual, can redistribute themselves in the liver, lung, and intestines of the recipient. Thus, disorders involving CNS deterioration are probably not appropriate candidates for treatment with bone marrow transplantation. The long-term outcome for an individual treated with this mode of therapy is still unknown. There is no question that the natural history of diseases treated in this way will be altered. A new set of complications will arise.*

As the authors also point out, bone marrow transplantation entails considerable risks of morbidity and mortality, as well as a large commitment of medical, financial, psychosocial, and other resources. A comprehensive evaluation and the presence of an HLA-identical sib are essential. Nevertheless, the morbidity or predictable mortality of the individual patient may be dramatically improved as in this reported case. This mode of therapy gives hope for previously hopeless disorders.

Growth Retardation in Crohn's Disease: The Merits of Aggressive Nutritional Therapy

Growth retardation, defined as a cessation or slowing of linear growth to a rate below that expected for age and pubertal stage, occurs in 30% to 85% of children with Crohn's disease of prepubertal onset.

The author reviews several possible reasons for growth failure. Malabsorption does not seem to be a significant cause since most growth-retarded children have normal D-xylose absorption and minimal fat malabsorption. Decreased nutrient intake has been reported, with anorexia being an important component of Crohn's disease as well. Many patients experience early satiety or abdominal pain after meals, thus making it necessary for them to eat small, frequent meals. However, not all observers have reported low nutrient intake in all growth-retarded children with Crohn's disease. Of the hormonal factors studied in these children, somatomedin-C has been low. Zinc deficiency also does not account for growth retardation in all patients. The role of enteric protein loss is not understood, but many growth-retarded children are in positive nitrogen balance.

While the exact energy and protein requirements of growth-retarded patients with Crohn's disease are not known, the home use of nutritional support permits intake of adequate energy and protein to restore growth.

The author offers four methods for nutritional intervention: (1) increased oral intake, (2) supplementary formulas, (3) supplementary parenteral nutrition, and (4) total parenteral nutrition. The method chosen should depend on the individual patient and his needs. Lactose intolerance could restrict the range of oral formulations, but the author suggests that this can be overcome by adding commercial lactase preparations to the formulas. In the author's own experience, increased growth velocity (amount not specified) occurred when the caloric intake was raised from a mean of 1,245 kcal/d to the recommended 2,400 kcal/d.

Kirschner BS: *Manual of Clinical Nutrition* (suppl)1983; 2(4):26.

Editor's comment—*This paper is a good review of state-of-the-art approaches to nutrition and growth retardation in Crohn's disease. While the ultimate cause of the poor growth remains unresolved, nutrition appears to be an important component. Nutritionally induced remission of the disease after bulk nutritional supplementation, as well as improvement in growth, has been documented. More must be learned about specific nutritional deficiencies, (ie, magnesium and zinc) and ways to deal with the patient's inability to ingest adequate calories for growth.*

MEETING CALENDAR

June 16-18 45th Annual Meeting and Scientific Sessions of the American Diabetes Association. Baltimore Convention Center, Baltimore, Maryland. Contact: Carolyn Sciortino, ADA, 2 Park Avenue, New York, NY 10016

June 19-21 67th Annual Meeting of The Endocrine Society. Baltimore Convention Center, Baltimore, Maryland. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814

June 22-25 Second Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology. The Hyatt Regency, Baltimore, Maryland. Contact: Dr. S. Raiti, Secretary, LWPES, 210 West Fayette Street, Baltimore, MD 20201

August 1-3 Clinical Genetics for Practitioners. Postgraduate Course. East Beach Conference Center, Kiawah Island, South Carolina. Contact: Division of Continuing Education, Medical College of Georgia, Augusta, GA 30912

In Future Issues

Genetics of Growth Hormone Deficiency by David L. Rimoin, M.D., Ph.D.

Growth Hormone and Chorionic Somatomammotropin: Gene Structure by John Parks, M.D.

Support Groups for Growth-Deficient Children by Judith G. Hall, M.D.

Robert M. Blizzard, M.D.
c/o Biomedical Information Corporation
800 Second Avenue
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Permit #391

GROWTH
Genetics & Hormones

Vol. 1 No. 3 September 1985

Genetic Forms of GH-Deficient and GH-Deficient-Like Dwarfism

Causes of short stature related to human growth hormone (GH) can result from a variety of genetic and acquired interruptions in the hypothalamic-pituitary-peripheral tissue axis. The various genetic types of pituitary dwarfism can be classified on the basis of: 1) the level of the defect; 2) the mode of inheritance; 3) whether or not there is an obvious developmental or degenerative disease of the hypothalamus or pituitary; 4) whether the pituitary deficiency is monotropic (isolated GH deficiency) or multitropic; 5) whether there is a mutation or deletion in the GH gene; and 6) in those cases due to a defect in GH action, whether somatomedin levels are normal or decreased.

This article will review the six currently recognized types of inherited GH deficiency (see Table), the possibility of a genetically inherited GH-deficient-like syndrome attributable to biologically inactive GH, some syndromes of inherited GH-deficient-like dwarfism (such as Laron dwarfism and pygmy dwarfism, which are characterized by the inability to generate insulin-like growth factors [IGF] in response to GH), and IGF-resistant dwarfism.

Two of the six types of GH deficiency are associated with multitropic pituitary hormone deficiencies (MPHD), and the other four are associated with isolated GH deficiency (IGHD). No familial crossovers between MPHD and IGHD have yet been reported.

Inheritance is autosomal recessive (AR) in one type of MPHD and X-linked recessive in the other. There is both interfamilial and intrafamilial variation of the associated hormonal deficiencies. In certain families with the AR type, one individual may lack all of the tropic hormones, whereas another may lack only GH and gonadotropins. Similarly, there may be variability in the hormonal responses to the hypothalamic peptides (GRH) and thyrotropin-releasing hormone (TRH) in sibships. Rogol et al recently reported studies in two sibships with three patients each. In *each* sibship, one patient responded to GRH with significant GH release and one responded to TRH with thyroid-stimulating hormone (TSH) release. This variability of response makes it difficult to determine whether the MPHD

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The Genes Controlling Growth Hormone Production, Secretion, and Action

Six peptide hormones normally participate in the regulation of growth hormone (GH) production, secretion, and action. These are GH-releasing hormone (GRH) and somatostatin or GH-releasing inhibiting hormone (GRIH) from the hypothalamus, two GH molecules (22K and 20K) from the pituitary, and two insulin-like growth factors (IGF-I and IGF-II) in the blood and some peripheral cells. During pregnancy, a seventh peptide hormone, human chorionic somatomammotropin (hCS), is produced and contributes to maternal GH activity. Advances in molecular genetics have made it possible to study the genes for each of these seven hormones. The purpose of this presentation is to discuss the chromosomal locations of the genes for each of these peptides, known abnormalities of the genes, and the consequences of those abnormalities.

Recombinant cDNA probes have been developed for GRH and GRIH. The former gene is located on chromosome 20 and the latter on chromosome 3. Preliminary studies have not disclosed examples of GRH gene deletion as a cause of isolated GH deficiency or multitropic pituitary hormone deficiency. Currently, GRIH is a gene without a recognized heritable disease phenotype.

All the genes for GH and hCS are

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In This Issue

Genetic Forms of GH-Deficient and GH-Deficient-Like Dwarfism

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is hypothalamic or pituitary in origin. Computerized tomographic skull scans were normal in two of the six patients. In the remaining four, the sella was either small or empty. Further studies using prolonged GRH stimulation might be helpful in elucidating the site of the lesion. The GH and GRH genes were present in the genomes of all six patients.

Zipf et al reported a third sibship in which MPHD was associated with X-linked recessive hypopituitarism. The deficiency of tropic hormones was variable, although GH and gonadotropin deficiency were constant. The authors suggested that the heterozygous state in the female does not result in any detectable abnormality. In this sibship, the mother had no easily identifiable X-chromosome genetic marker that would permit identification of the carrier state, such as XgA heterozygosity or color blindness. No restriction fragment length polymorphism (RFLP) studies have been reported in genetic MPHD, Type II. Since no clinical or endocrine differences exist between either of the two genetic forms of MPHD and the more common acquired form, genetic counseling is difficult.

Like MPHD, IGHD occurs much more frequently as a sporadic and acquired entity than as an inherited disease. Of the four currently recognized types of genetically inherited IGHD, only one (IGHD I-A) has been identified at this time with a demonstrable defect of the genomic material. Phillips et al studied nuclear DNA from eight individuals with IGHD I-A who were homozygous for DNA deletions varying in size from 6.7 to 7.6 kb, each of which included the hGH-N gene (see article by Parks on page 1).

IGHD I-A was described by Illig et al as AR and considered to be distinctive from other types of IGHD because of the total absence of circulating immunoreactive GH and the appearance of high concentrations of GH antibodies following GH therapy in these patients, rendering them GH-resistant. A number of families of different ethnic backgrounds have been described with this syndrome. Not all have developed antibodies and/or resistance to GH. An Argentinian child maintained a satisfactory response despite antibodies to GH. Several Israeli children with IGHD I-A did not form antibodies to hGH and their responses to treatment were as good as those seen in patients with other forms of GH deficiency. The originally described phenotype is not specific for IGHD I-A. A technique called Southern blotting for GH genes is required to establish the diagnosis.

IGHD I-B, also referred to as Type I, is inherited as an AR trait. Affected patients are hypersensitive to insulin and have glucose intolerance associated with insulinopenia. Puberty occurs spontaneously but is frequently delayed until the late teens or early twenties, and often appears abruptly during the first months of GH therapy. Rogol et al documented significant GH release following GRH administration, and Rimoin et al demonstrated normal GH-staining granules in the pituitary gland of an affected individual, suggesting that the basic defect is in the hypothalamus. Linkage studies utilizing RFLPs of the GH gene have not demonstrated a linkage in IGHD I-B. No abnormality of genomic material, including the GRH gene, was demonstrated by Rogol et al.

Patients with IGHD I-B usually grow spontaneously at rates that are slow but not as slow as the rates of patients with IGHD I-A or II. They also respond well to GH therapy. They usually do not exhibit the dramatic growth failure and/or phenotype of IGHD I-A and II and are hard to differentiate from those with acquired GH deficiency. Consequently, the genetic incidence is difficult to determine.

IGHD II was first studied by Rimoin and Merrimee in a family with three affected generations. Rogol et al restudied this family 20 years later, at which time a GH-deficient child had been born into the fourth generation. No abnormalities of the GH or GRH gene were observed. GRH administration produced no release of GH except in the 3-year-old in the fourth generation, whose GH rose to 3.6 ng/ml. When initially studied, this family had increased rather than decreased insulin response to glucose and arginine, as is usual for most patients with GH deficiency. However, there have been reports of families with dominant inheritance who have the insulinopenia and metabolic features of IGHD I. Therefore, Type II, as currently defined, is a poorly delineated autosomal dominant type of GH deficiency, and further studies in multiple families are needed to clarify the heterogeneity of the entity or entities.

IGHD III is an X-linked dominantly inherited type of GH deficiency. Fleischer et al initially described a kindred of two brothers and their two maternal uncles. These individuals had isolated GH deficiency and hypogammaglobulinemia. Two of the four had recurrent pulmonary infections that abated with gammaglobulin therapy. Three had panhypogammaglobulinemia and absent circulating B cells, and the fourth had normal IgA and IgM lev-

Table Genetic Growth Hormone Deficiency

	Inheritance	GH gene defect	GHRH gene defect	Comment
MPHD*				
I	AR	ND	ND	
II	X-linked	?	?	
IGHD†				
I-A	AR	hGH absent	Probably normal	Develop GH antibodies
I-B (or Type 1)	AR	ND	ND	
II	AD	ND	ND	
III	X-linked	?	?	• Hypo-globulinemia

*Multitropic pituitary hormone deficiency
†Isolated GH deficiency
AR = Autosomal recessive
AD = Autosomal dominant
ND = Not demonstrated

els but decreased levels of circulating B cells. T-cell function and number were normal. This kindred appeared to have a distinct X-linked recessive form of IGHD that was associated with hypogammaglobulinemia.

There have been reports of several patients with the clinical features of IGHD who achieve normal plasma immunoreactive GH levels following stimulation, who have low basal levels of IGF-I, and who respond to GH administration with normal IGF-I levels and a significant increase in growth rate. It was postulated that these individuals secreted an abnormal GH molecule that was biologically inactive, but immunologically cross-reactive. However, Phillips could find no trace of a defect in the hGH-N gene after careful DNA analysis in one such patient. He postulated that the hGH receptor in the liver rather than the hGH gene may be involved. In some of these patients, a deletion on chromosome 13, rather than on chromosome 17 where the hGH gene is located, was found.

Valenta et al recently reported a patient with normal levels of immunoreactive GH but decreased radioreceptor-assayable activity. This patient differed from those de-

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Address for Correspondence

Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

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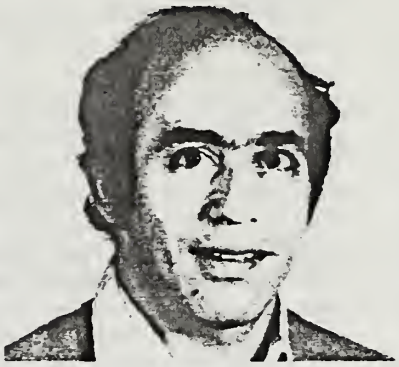

Alan D. Rogol, M.D., Ph.D.

Dr. Rogol is Professor of Pediatrics, Chief of the Division of Endocrinology and Metabolism, and Associate Professor of Pharmacology at the University of Virginia School of Medicine, Charlottesville. Before coming to Virginia in 1975, he served as a Lieutenant Commander in the Public Health Service.

A native of Seymour, Connecticut, Dr. Rogol received a Bachelor's degree in chemistry from the Massachusetts Institute of Technology in 1963. In 1970, he earned a doctorate in physiology from Duke University and his medical degree from Duke University Medical School, Durham, North Carolina. He served both his internship and two years of residency in pediatrics at the Johns Hopkins Hospital, Baltimore, Maryland. He was also (for two years) a fellow in the Clinical Endocrinology Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland.

Dr. Rogol is the author or coauthor of more than 80 journal articles, reviews, and other publications and communications. He is a member or fellow of several professional societies, including the American Academy of Pediatrics, the American Federation for Clinical Research, the Endocrine Society, the Society for Pediatric Research, and the Lawson Wilkins Pediatric Endocrine Society.

Associate Editor:

Judith G. Hall, M.D.

Dr. Hall has been Professor of Medicine and Pediatrics at the University of British Columbia and Director of the University's Clinical Genetics Unit at Grace Hospital, Vancouver, since 1981. For the previous nine years, she held similar posts at the University of Washington School of Medicine and the Children's Orthopedic Hospital in Seattle.

Born in Boston, Dr. Hall spent her teen years in Seattle. She returned to Massachusetts to attend Wellesley College, graduating in 1961. In 1965, she received a Master's degree in genetics from the University of Washington in Seattle and, in 1966, her medical degree from the University's School of Medicine. She returned East again, this time to Baltimore, for six years of postgraduate training. She served a mixed medicine and pediatrics internship at Baltimore City Hospital and a two-year fellowship in medical genetics at the Johns Hopkins Hospital. After a two-year residency in pediatrics at the Hopkins-affiliated Harriet Lane Home, Dr. Hall was awarded a one-year fellowship in pediatric endocrinology at Hopkins Hospital.

Author, coauthor, or editor of more than 350 articles, abstracts, case reports, books, book chapters and sections, book reviews, and other communications, Dr. Hall is a member of the Editorial Board of the *Journal of Clinical Dysmorphology* and a reviewer for numerous medical journals and research grant agencies. She is currently Vice President of the Society for Pediatric Research and a member of the Board of Directors of the American Society for Human Genetics.

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scribed above in that he had a normal plasma IGF-I level. However, when he was treated with exogenous GH, his growth response was excellent. Physical analysis of the GH in the patient's serum revealed a structural abnormality of the circulating GH, with most of the immunoreactive hGH migrating on gel filtration as large molecules.

These entities are probably heterogenous, but the extent to which gene defects may be present is as yet unknown. Further studies are needed to define the pathophysiologic mechanisms.

Two syndromes with inherited defects of IGF-I generation are recognized. The first is Laron dwarfism; the second, pygmy dwarfism. Clinically, Laron dwarfs resemble patients with IGHD except that their GH concentrations are normal or elevated. This autosomal recessive syndrome was first described in Oriental Jews, but has since been found in numerous other ethnic groups. These patients have severely pinched faces, high-pitched voices and, in affected males, small genitalia; growth retardation is severe. Early development is generally slow, fontanelle closure is delayed, and symptoms of hypoglycemia are frequent. Glucose intolerance is present with hypoglycemia and hypoinsulinemia. Plasma GH levels, however, are elevated, although they are normally suppressed with glucose. Plasma IGF-I concentrations are low and do not increase after GH administration. These patients are resistant to the growth-promoting effects of hGH administration.

Plasma GH appears to be qualitatively normal on the basis of serial immunoassay dilutions, electrofocusing, and molecular size distribution. Furthermore, substantial quantities of receptor-active GH have been found by radioreceptor assay. Using an erythroid progenitor technique, Golde et al found that Laron dwarfs had a specific cellular resistance to hGH. Liver cell microsomes from these patients do not bind hGH normally, although insulin does bind normally. Thus, the pathogenetic mechanism in Laron dwarfism appears to involve a defect in IGF-I and IGF-II generation that is probably secondary to a universal defect in GH receptors.

The African pygmy resembles the pituitary dwarf in size and skeletal proportions, but does not have the latter's truncal obesity, peculiar facies, and wrinkled skin. GH levels are normal in pygmies after insulin-induced hypoglycemia and arginine infusion, but like IGHD I patients, pygmies are insulinopenic and hypersensitive to the effects of exogenous insulin. They are completely unresponsive to the lipolytic, insulinotropic, and nitrogen-retaining properties of GH, and initial studies suggested that bioassayable somatomedin levels were normal. Thus, it was felt that short stature in pygmies was due to a peripheral unresponsiveness to somatomedin. Re-examination with the new IGF immunoassays, however, has indicated that pygmies have a primary deficiency of IGF-I, but normal levels of IGF-II. Furthermore, IGF levels did not increase following GH administration. A number of Caucasian patients with similar primary deficiencies of IGF-I have also been described, suggesting that individuals who clinically and metabolically resemble pituitary dwarfs but who have normal levels of immunoassayable GH should have their IGF levels and responsiveness to GH carefully evaluated.

Several patients with proportionate dwarfism, elevated IGF-I concentrations, and normal or elevated levels of circulating hGH have recently been described. These patients are said to have IGF-resistant dwarfism since IGF-I levels were elevated regardless of whether thay were determined by bioassay, radioreceptor, or radioimmunoassay. Cultured skin fibroblasts from a patient have shown a 50% decrease in IGF-I binding, suggesting defective IGF-I receptors as the cause of the IGF-I resistance. Whether or not there is a difference between patients with normal plasma GH levels and those with elevated levels has yet to be ascertained.

David L. Rimoin, M.D., Ph.D.

References will be sent upon request to Dr. Blizzard.

The Genes Controlling Growth Hormone Production, Secretion, and Action

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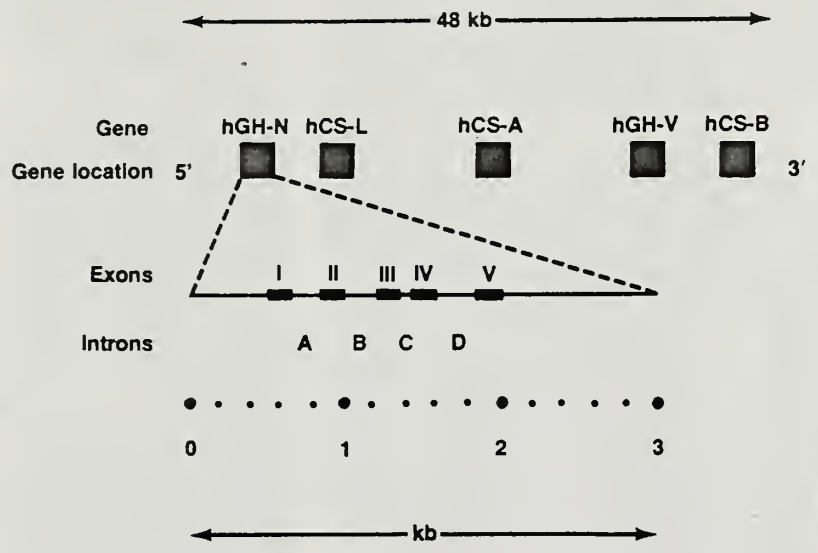
located on the long arm of chromosome 17. The five genes (hGH-N, hCS-L, hCS-A, hGH-V, and hCS-B) lie in the same 5′ to 3′ transcriptional orientation over a distance of 48 kb (one kb is 1,000 base pairs), as shown in the Figure. There is greater than 90% homology of the base sequences among these genes so that cDNA probes for either hGH or hCS recognize all members of the hGH and hCS gene cluster.

Each gene contains five exons (I to V in the Figure) that are interrupted at identical locations by four introns (A to D). The primary transcriptional products are premessenger RNA molecules with sequences representing both exons and introns. Intron sequences are excised and exons are spliced together to form mature messenger (m) RNA. Over 90% of the hGH premessenger is processed to form the mRNA for the 217 amino acid precursor of 22K hGH, which is the major GH molecule and has 191 amino acids. The remainder undergoes alternative splicing at the 3′ end of intron B to yield mRNA for a smaller 202 amino acid precursor of the 176 amino acid 20K hGH, which has less growth-promoting activity than 22K hGH. The hGH-V peptide has been produced in a heterologous expression system. It has a potency in the radio*receptor* assay similar to that of hGH, but it cross-reacts poorly with antibodies directed to hGH in the radio-*immunoassay*.

Homozygosity for a deletion within the hGH-N gene accounts for the GH deficiency in Type I-A isolated (IGHD). (See GH deficiency article by Rimoin on page 1.) The other four GH-related genes on chromosome 17 are intact. Prior to the discovery of this gene defect, Illig referred to the disorder as IGHD I-A, with the "A" referring to the blocking antibodies that affected patients tended to produce when exogenous GH was administered. The "A" now stands for absence of both gene and peptide. The pheno-



Regional map of the hGH and hCS gene cluster on chromosome 17 and the structure of the hGH-N gene in respect to exons and introns. Each of the genes has five exons and four introns.

type of postnatal growth failure indicates that the hGH-V gene expression, if it occurs, is not sufficient to promote normal growth in childhood.

The carrier state can be identified by restriction endonuclease analysis, a technique described in the addendum, which is available upon request. Since all patients with gene deletion do not have the phenotype initially described by Illig et al, and since all patients with this phenotype do not have a deletion of the hGH-N gene, examination for absence of the hGH gene—utilizing the Southern blotting technique—is indicated in siblings of patients with IGHD. This test is also useful in detection of carriers and in prenatal diagnosis.

Analysis of restriction fragment length polymorphism (RFLP) can also be used to determine whether hGH-N gene mutations analogous to those seen in β thalassemias could account for the decreased GH production seen in Type I-B IGHD and Type II IGHD. If this were the mechanism of the disease, then the affected children would have inherited the same hGH-N genes from their parents. In I-B IGHD pedigrees, the hGH and hCS restriction fragment sizes are normal, and a majority of affected sibling pairs are discordant for inheritance of hGH and hCS RFLP markers. Absence of linkage between hGH genes and disease shows that mutations causing I-B IGHD, and probably Type II, involve regulatory genes that are distant from the hGH-N gene.

The hCS-A and hCS-B genes share in the production of hCS, known also as human placental lactogen. They are expressed by syncytiotrophoblast cells of the placenta. The hCS-L gene is disabled by a single base change at the beginning of intron B. Substitution of an A for a G prevents normal splicing of premessenger RNA. Deletions have been described at the 3' end of the gene cluster. These produce an abnormal hormonal phenotype, but not a disease. One in 10,000 pregnancies is associated with the complete absence of immunoassayable hCS. A similar number of pregnancies have hCS levels of 1 μg/ml at term (normal = 3 to 9 μg/ml). Birth weights, lengths, and postnatal growth patterns have been normal. The mothers have had no difficulty in breast-feeding their infants. The explanation for absence of hCS in the maternal circulation is fetal homozygosity for deletions of the hCS-A, hCS-B, and hGH-V genes. Reproductive fitness in the absence of hCS production is not too surprising when viewed in the context of the evolutionary history of hCS. Complex GH clusters containing CS genes are a recent development. This pattern of gene organization is limited to primates. In other evolutionary lines, CS genes either do not exist or are derived from prolactin genes.

The genes responsible for IGF-I and IGF-II are located on chromosomes 12 and 11. They have not been studied extensively in growth disorders. An IGF-I gene abnormality is a possible explanation for the African pygmy phenotype and some other types of short stature associated with low IGF-I and normal or elevated hGH levels. The phenotype of isolated IGF-II deficiency has not been described. Somatic overgrowth in the Beckwith-Wiedemann syndrome may be related to the IGF-II gene. Some children with this syndrome have a partial duplication of chromosome 11 that may include the IGF-II locus.

Two future developments may be anticipated. The first is gene cloning to demonstrate subtle abnormalities in hGH-N gene structure (accounting for abnormal hGH efficacy or potency) as a cause of short stature. The second is the cloning of cDNA or genomic DNA fragments related to the hGH receptor gene. This gene is the most likely site for mutations causing Laron type dwarfism. We can expect that molecular genetic analysis will provide information about the causes of other growth disorders, and that its applicability to diagnosis, choice of treatment, and genetic counseling will increase.

John S. Parks, M.D., Ph.D.
Professor of Pediatrics
Emory University School of Medicine
Atlanta, Georgia

References supplied upon request to Dr. Blizzard. An addendum regarding RFLP and GH-related genes will also be sent upon request.

Dr. Parks is a guest contributor for this issue. In addition to his faculty appointment at Emory University School of Medicine, he is Director of Emory's Clinical Research Center.

Pituitary Growth Hormone and Creutzfeldt-Jakob Disease

All clinicians who have provided human growth hormone (GH) therapy to patients in the past need to be aware of the concern that has arisen during the last several months. There is the possibility that some batches of GH extracted from human pituitaries are contaminated with an infective agent that can lead to neurodegenerative disease.

Earlier this year, the National Institutes of Health (NIH) and the FDA were notified that a patient in California who had been treated with GH between the years 1966 and 1976 had died of a rapidly progressing degenerative neurologic disease and was found at autopsy to have typical changes of Creutzfeldt-Jakob disease (CJD) in his brain. CJD is a rare condition; it is usually sporadic and usually presents between 55 and 65 years of age, with a rapidly progressive degenerative course (cerebellar ataxia leading to death over six to 18 months) and with pathognomonic spongioform changes of the brain on autopsy. It is a transmissible disease that is very closely akin to scrapie in sheep and to a specific type of encephalopathy in mink.

CJD has been studied intensively for many years because, theoretically, it would be preventable if an infective agent could be isolated and treatment developed. However, the infective agent is elusive, and it is unclear whether the disorder is caused by a slow virus or by a subviral pathogen (a protein called a prion, which is a newly defined class of proteinaceous infectious particles thought to be capable of being infective without the presence of nucleic acid). The infective agent is also resistant to the usual sterilizing procedures, such as those using formaldehyde, alcohol, or glutaraldehyde, and even to fixation, but it is susceptible to bleach (1 mol/l NaOH and one hour in an autoclave at 120 °C). Currently, there is no therapy for CJD, and no remissions have occurred. The incubation period may be several decades.

Dr. Carleton Gajdusek at the NIH, who has been involved for many years in research on CJD, estimates that one to two people per million in the general population have changes characteristic of CJD in their brains at death. Because of the long latent period, as many as one in 6,000 to 10,000 people might carry the infective agent, although they may not manifest any symptoms. Thus, many of these people would die of other causes before CJD became manifest. GH has been produced by extracting between 5,000 and 16,000 pituitaries obtained at autopsy; there is a chance that one of these individual pituitaries carried the CJ infective agent, thus contaminating the entire lot. In North America, the average child on GH treatment will have received therapy for four years and will have received GH from several different lots. Thus, it is possible that many individuals treated with GH may have been exposed to the CJ infective agent.

Because of the potential implications of a transmitted neurodegenerative disorder in patients treated with extracted GH, several pediatric endocrinologists, officials from the NIH, the FDA, and the National Hormone and Pituitary Program (NHPP), as well as representatives of commercial suppliers of human growth hormone, assembled for an emergency meeting in April 1985. At about that time, it was recognized that two other patients who had been treated with GH had died of rapidly progressing neurologic degenerative diseases during the past year. One had not had an autopsy; the autopsy on the other patient was diagnostic of CJD. The incidence of CJD occurring in individuals under 30 years of age is less than one in 10 million; thus, to have three cases in one year in the United States, all of whom have had therapy with extracted GH, was a matter of great concern.

The technique for extracting GH changed dramatically in 1977. Prior to 1977, the method of extraction was relatively crude. It is important to point out that the three CJD patients all began their therapy before 1977 but were *not* all treated with GH from one lot. They overlap at least two extraction lots. The commercial companies and pituitary agencies in most countries feel that it is unlikely that a virus would be present in their material purified since 1977. However, CJ infective agent is not just any virus, but rather an unusual compound that is not yet understood. Thus, it is possible that even after 1977, extracted GH might be contaminated with the CJ infective agent.

The next question, of course, is: Will all individuals exposed to the infective agent develop the neurologic degenerative disease? There seem to be individual differences in response, both with regard to clinical presentation and length of incubation. However, as yet there is simply no answer to the question of who may develop the disease.

Because of this information and concern, in April of this year the FDA and the NHPP in the United States withdrew extracted GH for therapy of children who are GH deficient and for any other type of therapy, with the exception of children who have hypoglycemia as a result of their GH deficiency.

There have been more than 30,000 individuals treated with extracted GH since treatment programs began. What will happen to those individuals who were taken off GH therapy? They will stop growing temporarily and may have minor metabolic imbalances. However, it is well known that genetically engineered GH will be available for therapy within the next few months. It is anticipated that most individuals who have been off GH for a few months will have catch-up growth when restarted on therapy and will be minimally harmed by the hiatus in treatment.

Intensive investigation of the infective agent in CJD has been going on for many years. The application of molecular genetic techniques has allowed the isolation of the gene that produces the prion protein known to be associated with infectivity (if not the infective agent itself). This protein has been isolated and cloned. Interestingly, genetic information coding for the protein prion sequence is present in the normal human genome. However, it appears that the infective agent protein prion is more resistant to breakdown than the "normally" occurring protein. Through these investigations, it is hoped that we can develop the ability to diagnose infected individuals prior to symptoms and recognize which indivioual are at risk.

These events have spurred further investigation. First, as soon as the potential danger was recognized, GH from each extraction lot was injected into various animals (hamsters, monkeys, etc) known to be susceptible to the CJ virus in the hope of identifying batches that carry the infective agent. Second, research on the infective agent (in terms of developing potential therapeutic antibodies or therapies) is rapidly proceeding. However, the results of these investigations will not be available for months or years.

It has been known from previous work on CJD and related diseases such as kuru and scrapie that animals who have had repeated injections of infective agent do mount antibodies to the scrapie-associated fibrils and associated proteins (PRP 27/30). Obviously patients treated with potentially contaminated GH have had repeated injections. For this reason, researchers at the NIH would like to receive serum samples from patients who have been given GH in the past; they will let you know what they find in your specific patient(s). They will be testing for antibodies to scrapie-associated fibrils. To participate, send 4 to 5 ml of frozen serum collect by Federal Express to Dr. Joe Gibbs, Building 36, Room 4A17, NIH, Bethesda, MD 20205 (phone: 301-496-4821); include age of patient, during what years he or she was treated and for how long, how much GH was given, and the lot number, if known. Also, please notify Dr. Paul Brown, Building 36, Room 5B25, NIH, Bethesda, MD 20205 (phone: 301-496-5291) of any patients under your care who have received GH in the past, and who have neurological symptoms suggestive of CJ disease.

In summary, it is unclear what the future holds for patients who have been treated with extracted GH. However, it is important to be aware of the concern, to continue to be informed, to apprise patients and families of the situation, and to participate in any epidemiologic studies that are undertaken. In general, it is important to be straightforward and honest with patients, but to assure them that a great deal is being done to evaluate the situation and investigate the questions that remain unanswered.

Micropenis: (I) Adult Follow-Up and Comparison of Size Against New Norms; (II) Gender, Erotosexual Coping Strategy, and Behavioral Health in Nine Pediatric Cases Followed to Adulthood; and (III) Family Mental Health and Neonatal Management: A Report on 14 Patients Reared as Girls

In the *first paper*, Money et al review eight patients (22 to 31 years of age) with micropenis whom they have followed since early childhood. By definition, a micropenis is less than 2.0 cm (stretched length) in an infant. Seven of the patients had penises at least 2 SD below the mean and six were more than 3 SD below the mean. Five were treated during childhood with testosterone. Although penile growth occurred, it did not keep pace with body growth during puberty and adolescence. Thus, as young adults, all five again had a micropenis as compared with the average penile length in 65 normal adult males of 16.7 ± 1.9 cm, which was significantly higher than previously published figures. Mean length, which was determined to supplement this study, was similar in the normal men, regardless of race, height, body habitus, or sexual preference.

The authors conclude that testosterone treatment in childhood does not result in increased penile length in adulthood and that testosterone-induced enlargement of the infantile micropenis is an artifact of the induction of an adolescent growth spurt of the penis.

The *second paper* documents the coping strategies encountered in nine patients (the eight described in the first paper, plus one who had undergone a phalloplasty following testosterone treatment) followed into adulthood. The authors emphasize that there is no single syndrome of micropenis. Rather, a micropenis is a birth defect found in a variety of syndromes and having several etiologies. In a majority of cases, it is an isolated defect, with or without defective testicular function, and may result from hypopituitarism. The chromosomal karyotype is usually 46 XY, but occasionally may be 46 XXY, 46 XX, or mosaic.

During childhood, six of the subjects took precautions to avoid exposure during urination, and all avoided genital nudity. Despite precautions, five reported being teased viciously. Eight avoided juvenile sexual play. As adults, seven of the nine subjects were dissatisfied with the size and appearance of the penis. (The most extremely dissatisfied patient was the one who had undergone phalloplasty.) Of the remaining two patients, one had the second largest penis in the study. The other had multiple visible disfigurements characteristic of the Robinow syndrome.

As a strategy for erotosexual coping, several patients who needed exogenous androgen therapy for virilization deferred treatment and remained juvenile in appearance. Five were interested in sports and typical male activities as children. Teasing was minimal in this group and cross-dressing did not occur. Three associated more with girls than boys and subsequently had homosexual life-styles. Erotic inertia and deferred erotosexual participation with a partner were the most prevalent coping strategies in seven, and one initiated erotosexual contacts, but anticipated rejection. The remaining patient was the only one who took the initiative in erotic activity, relying on multiple partners and transient encounters.

Since four of the nine patients were associated with homosexuality and/or divergent sexual imagery, the authors hypothesize that having a micropenis may dislocate the normal juvenile experience of age-mate, rehearsal play, and imagery, and thus increase the chances that heterosexual orientation will be dislocated as well.

The *third article* describes 14 patients with micropenis who were assigned to the female sex. Ten were assigned by 12 days of age, and the other four by 29 months of age. Early decision is extremely important to avoid re-announcement of a baby's sex, always a crisis for the parents, regardless of their capacity to deal with it.

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The ignorance and/or reluctance of pediatricians, urologists, and obstetricians to diagnose micropenis and to advise accordingly was evident in the majority of cases. Although sexual deformities or malfunctions are still customarily considered stigmatizing in our society, it is still possible for many parents to cope, particularly with the help of professionals who can educate the parents and assist them in reaching a decision for gender assignment. The authors also emphasize that siblings are not usually included in the education process but should be.

Successful differentiation of feminine gender identity is contingent on the consistency of rearing the child as a girl, social determinants of gender role identity, and genital appearance. Female-appearing genitals can be created surgically during infancy. Late in adolescence, a coitally functional vagina can be created. Typically, there is no sacrifice of fertility, as sterility is likely to occur with micropenis. During adolescence, female hormones are administered so that the physique and appearance will be feminine.

The authors conclude that the functional morphology of the genitalia is a better criterion for sex reassignment than is the chromosomal or gonadal status. When a micropenis is vestigially small, it can be surgically reconstructed with vaginoplasty into a clitoris, whereas nothing can be done to make it coitally functional as a penis. Thus, a male baby with a micropenis can have a more satisfactory life as a girl and woman.

Money J, et al: (I) *J Sex Marital Ther* 1984;10:105; (II) *Compr Psychiatry* 1985;26:29; and (III) *J Prev Psychiatry* 1981;1:17.

Editor's comment—*These data have been awaited for a long time. They are in accord with the editor's belief that patients with micropenis can be reared more satisfactorily as females than males. The one possible exception may be the patients who have micropenis in association with growth hormone (GH) deficiency. We feel this group may be different and diverse. We have at the University of Virginia four such patients, all of whom are receiving GH. In two, the penis grew significantly while the remaining two continue to have micropenis.*

Growth Hormone Secretory Dynamics in Turner's Syndrome

Ross, Long, Loriaux, and Cutler have examined growth hormone (GH) output, somatomedin-C determinations, and bone ages in 30 patients with Turner's syndrome (TS), ages 2 to 20 years. The findings have been compared with those of 17 normal subjects, ages 4 to 17 years. The mean GH concentrations during day and night (specimens collected every 20 minutes), the peak amplitudes, and the peak frequencies were similar in girls with TS who were less than 8 years of age and in age-matched controls. The mean 24-hour GH levels in this group were actually higher in patients with TS than in controls (4.6 ± 0.7 ng/ml *v* 2.9 ± 0.2 ng/ml), although these values were not statistically significant.

TS patients who were more than 9 years old had lower mean GH concentrations during both day and night, compared with age-matched controls ($p<0.005$). Patients also had a significant decrease in the peak amplitude of GH release as compared with normals. Interestingly, when the TS patients between the ages of 9 and 20 were compared with each other, there was no significant difference between the day and night mean GH levels, peak amplitudes, or peak frequencies. Normal females in this age range have greater nocturnal elevation and amplitude, but not peak frequency.

All 21 patients with TS who were stimulated with arginine and insulin had peak GH concentrations >10 ng/ml. Serum IGF-1 concentrations were stated to be significantly decreased in those with TS between 6 and 12 years of age when compared with normals. However, none of the IGF-1 determinations was in the GH-deficient range.

The authors also present data indicating that bone ages are delayed in TS children of all ages. The delay in 14 girls, 6 to 10 years of age, was 1.4 yrs ± 0.3 SEM. The difference in bone ages between the normal population and the patients with TS increased during the adolescent years. The mean values for patients with TS, 11 to 17 years of age, were decreased by approximately three years, as compared with controls.

A significant increase in GH secretion during *normal* puberty has been observed in some, but not all, normal subjects. The authors propose that in these sexually infantile girls the role of estrogen would be consistent with the observation that integrated concentrations of GH did not increase at pubertal age. They also state that since short stature in children with TS is observed at all ages, the cause of short stature is most likely multifactorial. The authors conclude that a relative deficiency of GH in pubertal patients with TS may contribute to their adult short stature.

J Peds 1985;106:202.

Editor's comment—*The data presented are not surprising, but documentation that there is a difference in GH secretion between normals and patients with TS during the adolescent years is a significant contribution. Although many earlier studies in normal children do not indicate an increase of mean GH concentrations in normals at the onset of adolescence, recent studies utilizing testosterone in boys with constitutional growth delay strongly suggested that more GH is released in the presence of testosterone, and other studies suggest estrogen increases GH concentrations.*

In this study the authors found that the mean 24-hour GH determinations in their normal controls, 8 years of age and younger, was 2.9 ± 0.2 ng/ml, v 5.7 ± 0.8 ng/ml in the

9- to 17-year-old controls. The mean GH levels in TS decreased between childhood and adolescence from 4.6 ± 0.7 ng/ml to approximately 2.5 ng/ml. The difference in the secretion of GH by the girls with TS in the two age ranges is not statistically significant. The observed difference in the mean GH secretory rates, therefore, is primarily related to an increase in GH secretion in normal female adolescents and is not surprising.

The discrepancy of the somatomedin-C determinations during adolescence is also probably related to the absence of sex hormones in the TS patients. The authors found a mean level of approximately 0.85 U/ml for the 11 TS patients who were 11 years of age and older. If estrogen were administered to girls in this age group, the somatomedin-C levels would very likely increase and approach those seen in normal female adolescents.

That bone age is delayed in TS patients is also not surprising, since sex hormones contribute to skeletal maturation after the age of about 9 years. Patients with TS do not have sex steroids present, and, therefore, the clinical observation of delayed skeletal maturation discussed by the authors is expected.

Late-Onset Adrenal Steroid 3B-Hydroxysteroid Dehydrogenase Deficiency: (I) A Cause of Hirsutism in Pubertal and Postpubertal Women

The physical signs and symptoms, as well as abnormalities in glucocorticoid and mineralocorticoid hormonal levels, have been well documented in the "classical" forms of congenital virilizing adrenal hyperplasia. Within the past decade it has become increasingly clear that genetic defects of an adrenal steroidogenic enzyme such as 21-hydroxylase or 11-B hydroxylase can be manifested during *peripubertal* life and that the steroidogenic enzyme defect may be one of the causes of androgen excess in peripubertal and postpubertal women. In 21-hydroxylase deficiency, the mild enzyme defect manifested at puberty results from an allelic mutation at the 21-hydroxylase locus.

A mild defect in 3B-hydroxysteroid dehydrogenase (3B-HSD) in adult women with hirsutism has also been found and may not be recognized until later in life, when symptoms of excessive androgen production occur. Thus, it is possible that allelism at the 3B-HSD locus occurs and is responsible for a classical severe form that presents at birth, and for a milder nonclassical form that presents later in life and causes peripubertal-onset hirsutism.

The present study was conducted on 30 normally menstruating women (controls) and 116 postmenarchal women with either long-standing or slowly progressive excessive hair growth. None had ambiguous genitalia at birth by history. All had an adrenocorticotropic hormone (ACTH) stimulation test, and blood samples were analyzed for glucocorticoids, mineralocorticoids, sex steroids, and their precursors. Partial 3B-HSD deficiency was suspected in hirsute women in whom the Δ^5 precursors and the ratios of Δ^5 steroids to their reduced products all increased after ACTH stimulation to more than 2 SD above the mean for normal women.

Sixteen of the 116 hirsute women were classified as having nonclassical (partial) adrenal 21-hydroxylase deficiency based upon very low Δ^5-17 hydroxypregnenolone (Δ^5-17P) to 17-hydroxyprogesterone (17-OHP) levels following ACTH administration. An additional 17 hirsute women, including three sisters, met all criteria for partial adrenal 3B-HSD deficiency—the Δ^5-17P and dehydroepiandrosterone (DHEA) levels and the ratio of Δ^5-17P:17-OHP were all significantly elevated following ACTH when compared with normal women. These women were classified as having partial adrenal 3B-HSD deficiency.

Eighty-three of the 116 hirsute women had no apparent adrenal steroidogenic defect. Many had classical or other types of polycystic ovarian disease.

Women with partial 3B-HSD deficiency had an exaggerated diurnal variation in Δ^5-17P, with the major peak at 8 AM higher than in any of the normal women. These high levels of the Δ^5 steroids were readily suppressed with glucocorticoid therapy in those with 3B-HSD deficiency

In retrospect, of the 17 hirsute women with partial 3B-HSD deficiency, seven had final heights at least two to five inches below their parents' height. Five had pubarche between ages 5 and 8.5 years and six between 10.5 and 12 years. None had thelarche before pubarche. Reliable data could not be obtained from the other six women. The onset of hirsutism or acne in all 17 occurred between 12 and 20 years of age Baseline urinary 17-ketosteroid excretion was elevated in the majority, but was suppressed by dexamethasone therapy.

Pang S, Lerner AJ, Stoner E. et al: *JCE&M* 1985;60:428-439.

Editor's comment—*These data, along with those from several other laboratories, indicate that partial 3B-HSD deficiency is a common (approximately 12%) cause in this referral population of hirsute women. The most valuable hormonal tests in differentiating patients with 3B-HSD deficiency from normal women and from patients with variant 21-hydroxylase deficiency or hirsutism without an adrenal steroidogenic defect, are the ratio of Δ^5:Δ^4 steroids and the high level of precursor Δ^5 steroids after ACTH stimulation. ACTH stimulation and dexamethasone suppression, plus the characteristic adrenal circadian rhythm of the steroids, indicate an adrenal source of the elevated Δ^5 steroids due to partial 3B-HSD deficiency. Hirsutism in these women may result from the peripubertal conversion of Δ^5 steroids to Δ^4 steroids in situ at the target organ—for example, the hair follicle. The 83 women without defect in steroidogenesis probably represent a spectrum of ovarian disorders (many had cystic ovarian changes) that together represent the largest cause of peripubertal hirsutism.*

Since adrenal steroid biosynthetic disorders are readily treated, they should be considered during an evaluation by physicians who see female adolescents with severe acne and hirsutism.

Ketoconazole in the Management of Precocious Puberty Not Responsive to GnRH-Analogue Therapy

Precocious puberty is characterized by the intermittent pulsatile secretion of luteinizing hormone (LH) that reflects the episodic release of gonadotropin-releasing factor (GnRH or LHRH) from the hypothalamus. The pharmacologic principle employed therapeutically is that continuous infusion of GnRH (or the daily administration of a long-acting analogue) leads to subsensitivity (down regulation) of GnRH receptors on the gonadotrophs, thus annulling the release of the gonadotropins. Although most children with precocious sexual development will have the normal pubertal process turned on early (idiopathic precocious puberty), some boys have what appears to be autonomous Leydig cell function with low basal and GnRH-stimulated gonadotropin output (so-called testotoxicosis, or a form of gonadotropin-independent precocious sexual development). These youngsters would not be expected to respond to long-acting GnRH-analogue therapy.

The authors treated three such boys with the antifungal preparation ketoconazole. All had failed to respond to GnRH-analogue therapy. Ketoconazole treatment (200 mg every 12 hours) was started at least one month after discontinuation of the GnRH-analogue therapy. Within 24 hours, the testosterone concentrations fell significantly (less than 20 ng/dl in two of the three subjects). Measurement of 17-hydroxyprogesterone concentrations revealed an inverse relationship to testosterone concentration. There were no significant changes in the low urinary levels of gonadotropins. Basal cortisol concentrations were unchanged, but the peak response to adrenocorticotropic hormone (ACTH) was blunted. The testicular response to human chorionic gonadotropin (hCG) was also unchanged following ketoconazole treatment. Striking improvements in behavior were noted within the first 48 hours of therapy, with disappearance of erections and masturbatory activity.

With increasing dosages of ketoconazole, the behavioral gains were sustained and the testosterone concentrations remained low. The height velocity was significantly diminished from 15 cm/yr to 6 cm/yr.

Holland FJ, et al: *N Eng J Med* 1985; 312:1023-1028.

Editor's comment—*Most commonly, isosexual precocious development is due to central precocious puberty—that is, the normal pubertal mechanisms are activated too early. The efficacy of GnRH stimulatory analogue (agonist) therapy has been well documented. However, it is ineffective in patients with gonadotropin-independent sexual precocity. Ketoconazole was chosen because data suggest that this agent may interfere with testosterone biosynthesis through relatively selective effects on the C17-20 lyase step in steroid hydroxylation.*

These preliminary data, which show reductions in height velocity and in the rate of bone maturation, are promising for boys with gonadotropin-independent sexual precocity. Although ketoconazole therapy ought to be effective in idiopathic precocious puberty, it would appear that GnRH-analogue therapy is preferable—there is low toxicity and, by now, a good deal of experience. Although none of the boys exhibited hepatic toxicity to ketoconazole, treatment of adults with this hepatically metabolized agent has been associated with abnormalities in liver enzyme levels. Thus, for the rare disorder of testotoxicosis, and possibly for other forms of gonadotropin-independent sexual precocity, ketoconazole is logical and effective therapy. Because of the drug's potential hepatotoxicity and possible adrenal toxicity, patients being treated with it require intensive follow-up.

Infants With Birth Weights Less Than 1,001 g: Survival, Growth, and Development

At the University of North Carolina, 56 infants who weighed 1 kg or less and who were born in 1980 were cared for in the Newborn Intensive Care Unit. A surprising 52% survived the first year. Most of those who did not survive died during the first seven days.

Twenty-five infants were measured between birth and 16 months of age. Catch-up growth was apparent in many, but even when the growth plots were adjusted for age, 11 of 25 were below the fifth percentile for weight (four of the 11 were believed to be small-for-gestational-age infants). The heights appeared to be comparable to weights. Small head circumference at 12 to 16 months was closely related to low weight. Six of the 11 infants had chronic respiratory failure and five did not.

Development remains guarded, but optimism is reflected in the data. Twelve of 15 infants tested for hearing and language were found to be normal. Nineteen, including three of four survivors with birth weights less than 801 g, were free of neurodevelopmental difficulties, as defined in the study. They had physical and mental development indices of 86 or greater for their adjusted ages, and only two had permanent visual impairment. Four infants were mildly handicapped, and four were moderately to severely handicapped. A correlation between head circumference and a developmental handicap was apparent when the infants were tested at 12 to 16 months. The authors readily admit that the follow-up was short and that some children now classified as normal will probably be handicapped in the future, since learning disabilities cannot be predicted at this early age. Moreover, hearing deficits, now unrecognized, may subsequently become apparent.

Kraybill EN, Kennedy CA, Teplin SW, et al: *AJDC* 1984;138:837.

Editor's comment—*There is indeed reason for optimism. This group of patients and similar groups must be studied for an extended time. The editorial board will review this topic in further detail in future issues of this publication.*

Growth Patterns in the Hemoglobinopathies: (I) Growth Patterns by Age and Sex in Children With Sickle Cell Disease and (II) Growth and Sexual Maturation in Thalassemia Major

The first report evaluates by age and sex the growth patterns of 133 children enrolled in the Sickle Cell Anemia program at Children's Hospital in Pittsburgh. These children were representative of the total population aged 1 to 18 years with sickle cell disease (SCD) in the metropolitan area. Eighty-three children (62.4%) had homozygous sickle hemoglobin (SS) and 50 (38.6%) had a variant hemoglobinopathy, such as sickle-cell hemoglobin C disease (SC), sickle cell thalassemia (S-Thal), and sickle cell plus hereditary persistence of fetal hemoglobin (S-HPF).

The median height and weight of males fell below the 50th percentile at all ages between 2 and 18 years. Height and weight deficits increased with age, with values eventually falling below the fifth percentile in the 14- to 17-year age group. The median height and weight of female patients at ages 2 to 18 years followed a similar pattern, with median height and weight falling below the 50th percentile at all ages. A trend toward increasing deficits with increasing age was also seen. The overall growth deficit in the female patients was less pronounced at all ages. This basic growth pattern was seen in all patients with SCD (regardless of subtype), except for significantly higher weight in female patients with a variant hemoglobinopathy.

This study provides evidence of growth impairment in a large sample of children with SCD. The growth deficit, which increases with age, is more pronounced in males. Height and weight deficits appeared to begin as early as 2 years of age; the increasing deficits in height and weight noted in males between the ages of 14 and 17 years and in females between 10 and 12 years of age were associated with delayed onset of puberty. The authors constructed growth velocity curves that demonstrated the significance of the delayed pubertal growth spurt; maximum height and weight velocity occurred later and the magnitude of the spurt was depressed. Final adult heights of these patients were significantly decreased, with the mean height and weight of adult males falling below the tenth percentile.

In the second report, growth and sexual development were evaluated in 250 adolescents with β thalassemia major. These represented all patients above the age of 10 with transfusion-dependent thalassemia major who were receiving treatment at the thalassemia clinics of five teaching hospitals in northern Italy. Mean pretransfusion hemoglobin concentrations had been kept at greater than 9.5 g/dl during the previous five years and desferrioxamine had been administered for the previous seven to ten years. Thirty-seven percent of the thalassemic children were found to be 2 SD below the mean for normal height. After age 14 years, the percentage of children with short stature reached 62% for males and 35% for females. As in the normal population, thalassemic children with parents of short stature tended to be shorter than those with taller parents. Throughout childhood and adolescence, children with thalassemia were shorter than normal, but their weight was found to be adequate for their height.

Eighty-three percent of the males and 75% of the females had delayed skeletal maturation. Pubescent changes were absent in 30% of the females and 67% of the males between 12 and 18 years of age. Indeed, only 11% of females less than 18 years of age had experienced menarche. Cardiac arrhythmias were reported in 22% of the patients and cardiac failure in 5.6%. Several patients had diabetes, and thyroid function was frequently lower than normal.

Thus, growth retardation and delayed or absent puberty are common findings in children with transfusion-dependent thalassemia The authors suggest that patients with lesser iron levels because of more intensive chelation therapy do not fare any better than those on less adequate chelation therapy with regard to sexual maturation. Menarche does not seem to be any more prevalent today among girls between ages 12 and 14 who are on chelation therapy than it was in a group of female patients now older than 18, but not receiving adequate chelation therapy.

Phebus CK, Gloninger MD, Maciak BJ: *J Peds* 1984;105:28-33, and Borgna-Pignatti C, De Stefano P Zonta L, et al: *J Peds* 1985;106. 150-155.

Editor's comment—*As these two reports demonstrate, short stature and delayed adolescence are common problems in the hemoglobinopathies. This, of course, is true of all chronic disorders, be they hematologic, infectious, gastrointestinal, or cardiopulmonary in origin In transfusion-dependent thalassemia, however, much of the growth delay had been attributed to a defect in the hepatic biosynthesis of somatomedin and to iron deposition in the pituitary, resulting in deranged function of the hypothalamic-pituitary axis. Thus, hemosiderosis had been considered one of the major problems resulting in growth and sexual delay (and other endocrine problems) in thalassemia Hemosiderosis, however, was not significant in the sickle cell study, although growth was significantly retarded in the SCD subjects. It is clear from these studies that individuals with SCD do not achieve normal adult height, in contrast to earlier reports from Jamaica suggesting that adults with SCD may attain normal or even greater than normal height. The specific reasons for the poor growth and delayed sexual development in children and adolescents with SCD, however, are not clear.*

MEETING CALENDAR

October 9-12 American Society of Human Genetics Annual Meeting Salt Lake City, Utah. Contact: Ms. Gerry Gurvitch, Administrative Director, American Society of Human Genetics, 1550-B Monona Drive, Derwood, MD 20855 (301-424-4120)

October 14-18 37th Postgraduate Assembly of the Endocrine Society Sheraton Bal Harbour Hotel, Miami Beach, Florida. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-530-9660)

October 19-24 American Academy of Pediatrics. Annual Meeting San Antonio Convention Center, San Antonio, Texas. Contact: Division of Meeting Services, American Academy of Pediatrics, 141 Northwest Point Road, Elk Grove Village, IL 60007 (312-228-5005 or 800-433-9016)

December 6-8 Advances in Pediatrics II. Postgraduate course Focus on allergy, adolescence, learning disabilities, nephrology, and newborns. Williamsburg Inn, Williamsburg, Virginia. Contact: American Academy of Pediatrics, Division of Continuing Education, P.O. Box 927, Elk Grove Village, IL 60007

In Future Issues

The Syndrome of Psychosocial Abuse Dwarfism: An Update by Charles Annicello, Sc.D., and John Money, Ph.D. • The Use of Estrogens to Inhibit and Stimulate Growth by Jürgen R. Bierich, M.D.

Robert M. Blizzard, M.D.
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GROWTH
Genetics & Hormones
Vol. 1 No. 4 December 1985

Abuse or Psychosocial Dwarfism: An Update

Charles Annecillo, Sc.D., and
John Money, Ph.D.
Department of Psychiatry and
Behavioral Sciences and
Department of Pediatrics
The Johns Hopkins Hospital
Baltimore, Maryland

Abuse or psychosocial dwarfism is unique among syndromes of growth failure because it may be reversible. The child's failure to grow in stature, intellect, and social behavior because of abuse or neglect will persist irreversibly unless the child is rescued from the abusive environment. Sadly, the abuse usually occurs in the home.

Parents who abuse their children so contravene our society's idealization of the sanctity of the family that the evidence of abuse is either euphemized as discipline or, if that fiction cannot be maintained, prosecuted as a crime. Though child abuse is acknowledged in traditional children's literature, it is attributed to witches and wicked stepmothers; biological mothers are exonerated. A century ago, when society first recognized that children had a right *not* to be abused, "respectable" parents were not blamed for instances of child abuse, but parents who were illiterates, drunkards, prostitutes, or mental defectives were. Today it is known that parental child abuse cuts across social, economic, religious, and racial lines. Well-educated, nondrinking, pious parents of middle- and upper-class backgrounds may also be child abusers.

It is interesting to note that the victim in the first probable recorded case of abuse dwarfism was from a noble family. Kasper Hauser, the victim, was found abandoned in Nuremberg during the 19th century. Although 17 years of age when found, he was small and his speech was poorly developed. After he was rescued, his speech improved, as did his statural and social growth. He subsequently described years of confinement.

Causes and Classification

In the first half of the 20th century, the syndrome of abuse dwarfism was synonymous with maternal deprivation and hospitalism, even though height and weight measurements were not reported. Data on the syndrome of hospitalism were from investigations of institutionalized infants and children

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The Use of Estrogens to Inhibit and Stimulate Growth

Jürgen R. Bierich, M.D.
Associate Editor—Growth, Genetics and Hormones

Introduction

Estrogens exert a dual action on growth: small doses stimulate and high doses inhibit. While treating tall girls with high doses of the hormone is generally accepted today, low-dose therapy for retarded growth is still considered investigational and requires further study.

Inhibition of Growth With High Doses of Estrogens

The use of high-dose estrogen therapy for growth inhibition goes back to Goldzieher (1956), who treated 14 excessively tall girls with 2 mg/d of stilbestrol. Since then, numerous variations of this approach have been applied by many investigators. However, the use of stilbestrol, an artificial estrogen that does not occur in nature, has been completely abandoned since it became apparent that it may induce vaginal carcinomas in female offspring if taken during pregnancy. The stilbenes will therefore not be discussed further in this article.

A number of studies assessing estrogen treatment for growth disorders have been conducted since 1962. Most of the data concern girls in whom therapy commenced at age 12 to 13 years, and thus present valid comparable observations. A mean estrogen-mediated height reduction of 4.5 cm was achieved within an average of 23 months.

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In This Issue

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who exhibited characteristic behavior patterns and unresponsiveness despite adequate nutrition and medical care. Classical descriptions of this hospitalism syndrome were written by several groups.

Dwarfism undoubtedly has occurred under conditions of abuse and neglect in institutional settings. However, abuse dwarfism is typically recognized as occurring in the home. Paradoxically, the hospital provides a positive environment with good medical care, nutrition, and sleep, and the advantages of one-to-one "parenting" and education from a concerned staff.

When abuse dwarfism was recognized as a syndrome during the 1960s, investigators speculated that the chief etiologic factor might be maternal and/or emotional deprivation. This was consistent with the concepts and nomenclature developed by Spitz, Bowlby, and Ainsworth. However, two of the early papers on the syndrome by Powell et al concluded that emotional deprivation was the appropriate diagnostic designation. Before the identification of the specific diagnostic link between child abuse and reversible dwarfism, there were various terms for the syndrome—namely, environmental failure to thrive, deprivation dwarfism, psychosocial failure to thrive, and psychosocial deprivation dwarfism. Taxonomically, the syndrome today is usually known as abuse dwarfism, or psychosocial dwarfism.

The range of abuse inflicted on victims of abuse dwarfism includes disturbances of various intrusive and deficient sensory stimuli, particularly those related to isolation, food restriction, and direct trauma to the body. Adverse stimuli in the abusive environment presumably affect loci in the CNS that control statural growth. Discontinuance of abuse is accompanied by neurochemical changes that improve growth.

Catch-Up Growth After Rescue

The components of growth failure persist and eventually become irreversible, unless the child is rescued from the abusive environment. The earlier the rescue from abuse, the greater the amount of physical, mental, and behavioral catch-up growth that will be achieved. Many patients have shown dramatic catch-up growth even though their adult height fell below the mean for the general population. Of the 50 patients on record in the Johns Hopkins Hospital psychohormonal research unit, the two most severely affected dramatically exemplify the reversibility of statural growth impairment, but only to a degree. Following rescue, one boy (rescued at age 16) grew 13 inches in three years. The other patient, a girl rescued at age 8, grew 10.5 inches in only one year. However, their final adult heights were 5′4″ and 4′10 1/2″ respectively. (The average adult height is 5′10″ for males and 5′5″ for females.)

Dramatic improvements in intellectual growth have also occurred following rescue. The greatest magnitude of change, from an IQ of 36 to an IQ of 120, occurred in a girl who was tested initially at 3 years, 8 months and subsequently at 13 years, 11 months. She was among 23 patients who qualified for an investigation of IQ change among abuse victims with various periods of persistent and continuing rescue. At rescue, the average IQ was 66 and, after different periods of persistent rescue for each individual, the average IQ for the group was 90. The change represents an average shift from mental retardation to normal intelligence. The longer the time in rescue, the greater was the increase in IQ (Table 1). In general, the findings revealed persistent impairment of IQ associated with abusive environments, in contrast to improvement of IQ in rescue environments even when rescue was found to be only partially satisfactory.

The question of whether permanent impairment of intellect could occur was addressed in an investi-

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Table 1 IQ Elevation After Rescue (N = 23)

IQ	Before rescue	After rescue	Increase in IQ	Age before rescue*	Age after rescue*	Increase in age*
Mean	66	90	24	7, 7	12, 8	5, 1
SD	16	21	21	4, 7	5, 11	3, 1

r = 0.78; P < 0.005
**Age in years, months*

Table 2 IQ Elevation After Rescue: Younger and Older Patients (N = 14)

Age at rescue	Baseline IQ*	Follow-up IQ*	IQ elevation*
<5 1/2	71 ± 21	104 ± 11	33 ± 24
>5 1/2	63 ± 15	78 ± 16	16 ± 7

** Mean ± SD*

Table 3 Means and Correlation of IQ and HQ Increments Accrued During Follow-up (N = 32)

Follow-up status	IQ*	Height quotient
Before rescue	69 ± 17	55 ± 17
After rescue	88 ± 18	82 ± 11
Difference	19 ± 22	27 ± 18

r = 0.42; P > 0.01
**Mean ± SD*

gation of IQ change that compared younger *v* older patients. The younger the age at rescue, the greater the gain in IQ (Table 2). Each group had the same amount of time for catch-up change in IQ.

Skeels published a history-making monograph in which he described the outcome of a controlled study of a permanent and gross degree of mental retardation as a sequel to infantile institutional abuse and neglect. Dennis, in *Children of the Crèche*, further demonstrated that intellectual growth was stunted and the IQ permanently reduced by as much as 50% as a sequel to uninterrupted, life-long institutional abuse and neglect. For those institutionalized foundlings who were adopted and integrated into normal family life, the earlier the adoption, the earlier the resumption of normal intellectual growth and the higher the ultimate level of adult IQ.

The correlation between child abuse and a reversible failure of statural and mental growth was first ascertained at Johns Hopkins in a longitudinal follow-up of a severely affected patient. However, until 1983, there were no systematic statistics on the specific relationship between the rates of intellectual and statural catch-up growth. At that time, height quotients (HQ) were compared with intelligence quotients (IQ). Arrested and subsequent catch-up growth in stature were compared with arrested and subsequent catch-up growth in intelligence. Growth in both areas caught up at similar rates (Table 3).

The odd or antisocial behavior that abuse victims often exhibit—for example, eating from garbage cans, drinking from toilet bowls, and excessive eating and drinking, possibly followed by vomiting—is also reversible upon rescue. Other reversible behavioral symptoms include enuresis, encopresis, social apathy or inertia, crying spasms, insomnia, eccentric sleeping and waking patterns, pain agnosia and self-injury, all of which occur in the growth-retarding environment of abuse.

After children are rescued from abuse, their sleep characteristically changes from poor to good. This change correlates with a measured increase in statural growth. Interestingly, secretion of plasma human growth hormone (hGH) consistently relates to slow wave sleep and synchronized deep sleep stages (EEG stages 3 and 4) in normal children. Findings by Taylor and Brook in 1984 revealed that the postrescue reversal of stage 4 sleep impairment was associated with improvement in both hGH secretion and statural growth in a group of patients with abuse dwarfism.

Hyporeactive response to pain, or pain agnosia, is another phenomenon that reverses following rescue. Prerescue reports from parents and others note that the children did not complain, cry, or shed tears when punished, and generally did not react or complain when hurt, injured, or venipunctured.

Social maturation in children with abuse dwarfism is also retarded so that social age, including academic age and psychosexual age, is deficient. Although measurement problems exist, a project is under way to investigate psychosexual development in a small group of older patients.

Endocrine Function and Reversibility

Modern genetic theory avoids dichotomizing genetic and environmental factors and postulates a genetic range of reactivity that responds to prescribed environmental cues. Factors that influence statural, intellectual, and sociobehavioral growth are implicit in the social environment. Child abuse constitutes one environmental factor that constricts the prescribed environmental boundary and inhibits its growth. Rescue from abuse may release the inhibition and widen this boundary.

Some of the hypothalamic/pituitary details of how growth is arrested and then resumed have been specified. Under conditions of abuse, the pituitary gland and probably the hypothalamus become dormant and hormonally hypofunctional. It fails to secrete growth hormone (somatotropin). If abuse continues until the expected time of puberty, the gonadotropic hormones (LH and FSH) are not secreted. Thus, the ovaries or testes fail to secrete their own sex hormones, and sexual maturation lags. To a lesser degree, pituitary secretion of adrenocorticotropic hormone (ACTH) is also suppressed, but usually not lethally. It is reasonable to postulate that hypothalamic releasing hormones may be suppressed or that somatostatin is excreted in excess.

Knowledge about the influence of hypothalamic hormones or derivatives on learning and retention of learned facts in animals is accumulating rapidly. Neurohormones such as ACTH and MSH (melanocyte-stimulating hormone) and/or neurotransmitters such as β-endorphin may govern both hormonal secretion from the pituitary and growth of intelligence. Consequently, both pituitary secretion and growth of intelligence may be arrested in response to the external, socially imposed stimuli of child abuse and neglect.

The social mediation in this syndrome is evident in the interactions between the parents and the child, particularly with respect to pathological behavioral dynamics on the part of the parents. Both parents often collude as child abusers and frequently lie about how the symptoms of abuse occurred. The mother typically initiates abuse but cannot give a rational explanation for doing so. A study of the family dynamics in two severely affected patients re-

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Address for Correspondence

Please send all correspondence to Robert M. Blizzard, M.D., Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908.

Growth, Genetics, and Hormones is published by Biomedical Information Corporation under an educational grant from Genentech, Inc. The information in this publication reflects the views of the editors and does not necessarily reflect the opinions of the sponsor or the publisher.

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Abuse or Psychosocial Dwarfism: An Update

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vealed that the mothers had a "sin" that was symbolically being atoned for or expiated by the sacrifice of their children. In both cases, the "sin" pertained to the mothers' own births out of wedlock; in one case the birth was a sequel to incest.

Impaired growth persists as long as the child is sacrificed as a proxy to atone for the mother's feelings of guilt. Interestingly, even after the abuse is removed, a dependency or even addiction to abuse persists in most of these children. Addiction to being abused helps to explain a victim's resistance to amelioration and cure.

One of the justifications used by abusing parents is that their child instigates abuse. This claim may signify a failure of parent-child bonding, even from birth onward. Subsequently addicted, the abused victim responds to abuse by stimulating more of it. The neurochemistry of this addiction theoretically could be linked to the neurosecretion of a brain endorphin with a morphine-like sedative effect. This morphine-like effect might be helpful in explaining the presence of pain agnosia before rescue and why abused children incite their rescue caretakers into being abusive after rescue.

What is still needed is an explanation of how forbidden and repugnant behavior becomes endorsed and practiced. For so complete a reversal of turning the repugnant into a sanctioned practice, Solomon formulated and tested the theory of opponent-process learning. Opponent-process learning is seen in action when fear and terror are converted into a daredevil act or when the tragedy of being abused is turned into the exhilaration of seeking abuse. Opponent-process learning also explains how apparently decent parents self-righteously justify their abusive behavior and perpetuate themselves as abusers.

The syndrome of abuse dwarfism has profound heuristic and theoretical importance for medical practitioners. It exemplifies, in the human species, the way that stimuli from the external social environment may act in concert with internal physiologic functions to program—or arrest—growth and development. The syndrome should be considered in the differential diagnosis of short stature whenever a child presents with a combination of short stature for age, IQ deficit, learning disability, and odd or bizarre types of behavior.

References will be sent on request to Dr. Blizzard.

Drs. Annecillo and Money are guest contributors for this issue. They are internationally respected as authorities in psychosocial dwarfism.

The Use of Estrogens to Inhibit and Stimulate Growth

continued from p. 1

Which factors predict successful treatment? The dosage of the estrogens is significant, as are a number of interrelated auxologic factors, such as chronological age, bone age, onset of menarche in the subject at the start of treatment, and the subject's so-called "growth potential." The last factor is the difference between height at the start of therapy and the predicted final height.

Relatively low doses of estrogens were given to 12- to 13-year-old patients by Bayley et al (1962), Frasier and Smith (1968), Neugebauer (1974), Colle et al (1977), van der Werff ten Bosch and Bot (1981), and Schambach and Nitschke (1985). In these patients, an average growth reduction of only 2.4 cm was attained, an unsatisfactory result. Better results, ie, a mean reduction of 7.2 cm, were achieved by Kuhn et al (1977), von Puttkamer et al (1979), Willig et al (1980), and Bierich (1978, 1983). Kuhn et al and Willig et al gave a dose of 0.5 mg/d of ethinyl estradiol, while von Puttkamer et al and Bierich gave a dose of 7.5 mg/d of conjugated estrogens. These dosages are currently recommended for the treatment of tall stature.

Age and Maturity at the Beginning of Treatment

According to Bayley and Pinneau, 10-year-old girls still have 13.8% of their height potential, while 13-year-old girls have only 4.2% left. Consequently, during the three years between 10 and 13, the growth rate is reduced by 9.6%. Whitelaw and Foster (1962) were the first to draw attention to the importance of age and the necessity for early treatment. The same has been demonstrated by Greenblatt et al (1966), Zachmann et al (1975), Kuhn et al (1977), Bierich (1978), Andersen et al (1980), and John and Schellong (1980). Starting therapy early increases the growth-inhibiting potential of high-dose estrogen. In most cases, estrogen therapy was started in the second and third Tanner stage of puberty.

A number of investigators, however, recommend that treatment be started prior to puberty. Among them are Whitelaw and Foster (1967), Reeser et al (1979), and Schambach and Nitschke (1985). Based on reports from the two latter groups, it is apparent that one can treat prepubertal girls with much lower dosages of estrogens than those used in postpubertal girls. Reeser et al (1979) recommended only 0.2 mg/d of ethinyl estradiol, while Schambach and Nitschke recommended only 0.08 mg of mestranol. These investigators specifically intend to avoid the possible risks associated with the use of supraphysiological doses of estrogens. However, one has to cope with a mild form of precocity if the treatment is started prior to spontaneous sexual development.

Side Effects

Three major side effects of high-dose estrogen therapy will be considered here: development of neoplasms, infertility, and thromboembolism.

Malignancies, which often develop in older women receiving es-

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trogens, are not encountered in adolescents. Carcinomas of the endometrium have been observed only in patients with Turner's syndrome who were treated continuously with estrogens alone (Levine, 1978). As long as the endometrium is periodically shed (the result of exogenous progesterone), development of precancerous atypia such as cystic glandular hyperplasia can be avoided. Therefore, progesterone (eg, 10 mg of medroxyprogesterone acetate) is routinely given during the last week of each four-week cycle, while estrogen is given continously throughout the cycle.

Suppression of the gonadotropins is substantially limited to the period of treatment, and spontaneous menstruation recurs two to three months after therapy is discontinued. Adverse effects on subsequent fertility have not been reported. Persistent amenorrhea is extremely rare.

The acute risk of thrombosis is a matter of concern. It is well known that adult females using oral contraceptives are at higher risk for developing blood clots. The accelerated coagulation of the blood is caused primarily by the estrogen-dependent reduction in antithrombin III. Blombäck et al (1983) also found a significant lowering of antithrombin III in adolescent girls treated with high-dose estrogen. If conjugated estrogens are given, however, these alterations in clotting factors do not seem to occur (von Petrykowski and Schmidt, 1983).

It is important to note that only one instance of thrombosis was reported in a large-scale inquiry conducted by Conte and Grumbach in 1978. That study analyzed data from 904 patients who were treated with estrogens for tall stature.

Mode of Action

Based on the favorable results of estrogen treatment in acromegalic patients, Goldzieher (1956) hypothesized that estrogens suppress the somatotropic function of the adenohypophysis, ie, human growth hormone (hGH). Actually, the opposite is the case. With estrogen treatment, basal and stimulated hGH secretion increase. The specific action of estrogens primarily involves somatomedin, not growth hormone itself. Wiedemann and Schwartz reported in 1972 that estrogens decreased the sulfation factor (the biologically active somatomedin) in serum in acromegalic patients. Von Puttkamer et al (1977) showed that serum somatomedin concentrations were markedly lowered in tall girls who received high doses of estrogens for months. After six months of treatment, the levels were only 57% of pretreatment values. These findings were confirmed in 1981 by Gourmelen et al. They explain that reduced growth velocity in girls with open epiphyses may be due to the decrement of serum somatomedin concentration, and not to a mechanical barrier that prevents longitudinal bone growth, although the latter possibility is not excluded.

Promotion of Growth With Low Dosages of Estrogens

The natural model of growth promotion by estrogens is the pubertal growth spurt (PGS) in girls. Although growth velocity is slow prior to puberty, it reaches a maximum of approximately 8 cm per year during the course of puberty. This rapid increase in height precedes men-

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Letter From the Editor

Dear Colleague:

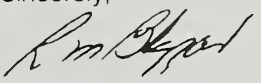
For the past six months, while human growth hormone (hGH) has been unavailable, there has been anxiety expressed by parents of GH-deficient (GHD) children that their children have been without treatment. Parental concern was partially alleviated on October 18, 1985, when the Food and Drug Administration approved a biosynthetic GH (Protropin®, Genentech, Inc.) for the treatment of children with GHD. This hormone will be available by prescription through pharmacies at hospitals where GHD children are typically treated.

The present formulation was tested in clinical trials in the United States and was demonstrated to be effective in stimulating growth in GHD children. Testing was done in 84 GHD children who received intramuscular injections three times per week at a dose of 0.1 mg/kg (0.2 IU/kg) for six to 36 months. Although antibodies developed in approximately 30% of the children, only one patient developed antibodies of the type and titer that produced slowing of growth (ie, antibodies associated with high GH-binding capacity). This patient subsequently responded to native hGH treatment with accelerated growth. No adverse effects of antibody formation on the immunological, cardiovascular, and renal systems were demonstrated.

Since this hormone is manufactured by a recombinant DNA process, there is no concern about contamination with the slow virus that causes Creutzfeldt-Jakob disease—the reason that native GH was withdrawn from distribution earlier this year. Recombinant DNA technology also ensures virtually limitless supplies of DNA biosynthetic GH, thus making it possible for all GHD children to be treated.

Physicians providing medical care to children should make every effort to identify—and provide proper evaluation and treatment for—GHD children. However, as a pediatric endocrinologist with many years of experience, I am concerned that this hormone may be abused and given indiscriminately to children who may or may not benefit from it. Hopefully, physicians will resist the pressures to prescribe GH for children who have not been adequately diagnosed as GH-deficient.

Sincerely,



Robert M. Blizzard, M.D.
Chairman, Editorial Board

The Use of Estrogens to Inhibit and Stimulate Growth

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arche by at least a full year. PGS is absent in girls with gonadal dysgenesis. Possibly, this is because ovarian estrogens are not produced. Consequently, it has been discussed exhaustively whether the androgens from the adrenals cause the PGS in females. Today we know that PGS follows the onset of increased adrenal androgen secretion by a period of four to five years and correlates better with gonadarche. Another clinical indication of the determining role of the estrogens themselves is the normal adult height and the normal PGS in patients with testicular feminization (Zachmann et al, 1984). These "hairless" women or girls with a 46 XY karyotype produce in their testes large quantities of testosterone; however, since they have no androgen receptors, the androgens cannot exert their characteristic actions. Consequently, the PGS in females is primarily derived from estrogens.

Studies evaluating physiologic dosages of estrogen during puberty have been conducted by Rosenfield et al (1974, 1980). The investigators gave 1 to 2 mg depot estradiol intramuscularly per month to nine patients with Turner's syndrome who had an average chronological age of 15.9 years and a bone age of 12.5 years. This therapy led to normal sexual development and doubled the growth velocity and bone age velocity. During treatment, the serum somatomedin level rose markedly, resembling the normal pubertal increase. This finding is in sharp contrast to the reduction in somatomedin concentration to high doses of estrogens.

The question of optimal estrogen dose for the promotion of growth has been studied frequently in recent years. How low must the dose be if it is to stimulate growth? Interestingly, doses as low as 0.05 mg ethinyl estradiol and 1.25 mg conjugated estrogens (hitherto applied as replacement therapy doses) are capable of inhibiting longitudinal growth. According to van der Werff ten Bosch and Bot (1981), growth velocity can be reduced by as little as 0.05 mg ethinyl estradiol.

Levine-Ross et al (1983) have correctly pointed out that peak height velocity during puberty does not occur at the time of menarche, but usually one year earlier. At this time estradiol concentration in plasma is approximately 20 pg/ml, or one sixth the adult level. These investigators measured the growth of the ulna in patients with Turner's syndrome who had received different estrogen regimens and determined that 100 ng/kg body weight was the optimal dose. The favorable results of the first short-term trials have since been confirmed by investigations of six months' duration. Other studies in which the same doses of estrogens were given produced similar results [Saghedi-Nejad et al (1984), Alexander et al (1984), and Rosendahl et al (1985)]. However, in all these investigations, the observation period was not long enough to draw any final conclusions or to make any definite statements on ultimate adult height.

Mode of Action

How do low doses of estrogens stimulate growth? Aside from the enhancement of adrenal androgen synthesis, four principal interpretations are possible:

- Estrogens increase the secretion of hGH
- Estrogens stimulate growth *per se*
- Estrogens work synergistically with hGH
- Combinations of the above

During sexual development, spontaneous nocturnal hGH secretion increases in both sexes to levels that are more than double the prepubertal values (Finkelstein et al, 1973; Bierich et al, 1985). Also, the conventional provocation tests for hGH induce considerably higher peaks after puberty (Frantz and Rabkin, 1965; Frasier et al, 1970) than before. These changes can be explained by a "priming" of the hypothalamus or hypophysis with the sex hormones. The well-known rise of serum somatomedin-C concentration during puberty is a sequel of the increased hGH secretion.

In the investigations of Levine-Ross et al, the greatest ulnar growth was seen with 100 ng/kg/d of ethinyl estradiol while the somatomedin levels reached their maximum with 800 ng/kg. This might indicate an estrogen-mediated, somatomedin-independent mode of growth stimulation.

In the male, the pubertal growth spurt is effected through two independent mechanisms: the androgen-stimulated hGH increase (see above) and a functional synergism between androgens and hGH (Zachmann et al, 1975). Androgens on their own may not stimulate growth. It can be presumed that a corresponding synergism also exists with regard to estrogens. Von Puttkamer et al (1977) reported on clear cut increments of spontaneous hGH secretion in tall girls receiving estrogen.

Additional mechanisms, which are not clear, may also play a role in the stimulation of growth by estrogens.

In summary, estrogens can stimulate or inhibit growth and can be used effectively in both instances. However, attention must be paid to the age of the patient, the type of estrogen used, and the dosage applied. Side effects of estrogen therapy for stimulation or inhibition of growth are minimal.

In Future Issues

The Genetics of Insulin-Dependent Diabetes
by Noel Maclaren, M.D.

The Effect of Insulin Control on Growth, IGF-I, and Growth Hormone
by William Tamborlane, M.D.
and Stephanie Amiel, M.B.

Support Groups for Families of Children With Growth Problems

Judith G. Hall, M.D.
Associate Editor—Growth, Genetics and Hormones

Lay and support groups concerned with specific disease entities have blossomed in the past few years. Support groups for families of children with growth disorders have been active and productive. The purpose of this article is to make physicians who care for children with growth problems aware of these organizations and the resources they provide to families and other health professionals.

In general, there are five reasons why lay or support groups develop. First, they provide information and practical advice for the families and allow them to share personal experiences about specific conditions. Such groups can play an important role in helping a family adjust to the fact that they have a child with special needs. Second, the groups strive to educate the general public and physicians about these conditions. Many families have felt the frustration of not being able to find physicians who were knowledgeable about the rare conditions affecting their relatives. Supporting and advocating related medical research is the third reason. The fourth is to help provide care, therapy, and/or educational opportunities for affected individuals. The fifth reason is to provide an opportunity to socialize. Affected individuals and family members who face the same problems and share common experiences often become friends who wish to share their social experiences and good times together.

Several lay groups are described below. Most charge minimal membership dues and provide newsletters about recent developments in the area of interest. The newsletters usually include useful tips, a social calendar, and an update on other members. Most groups also raise money to promote research or to provide scholarship funds or medical care for affected individuals. Many publish outstanding booklets that are excellent sources of information for families and physicians, who especially need to be aware of such groups in order to refer families and to utilize their resources. Physicians often play a critical role in guiding families to groups that can allow positive utilization of potentially hostile energy. Physicians should contact their local university-based genetics services for the names of other specific disease-related groups.

Little People of America (LPA) is a nationwide, voluntary organization dedicated to helping people of short stature. LPA is divided into districts (by geographic region) and smaller area chapters. Regional meetings, an annual national meeting, and a number of less formal gatherings are held periodically. The organization was founded in 1957 when the television and movie personality, Billy Barty, planned a meeting for short-statured individuals like himself in Reno, Nevada. Today, LPA has more than 4,000 members from all walks of life who are 4'10" or less.

Special needs for specific groups within LPA were recognized soon after its founding. A teen group and a group for young single adults were organized. The concerns of adult members prompted organization of committees and workshops on careers, exercise and fitness, nutrition, continuing education, social attitudes, and marriage and family counseling. An adoption committee finds adoptable short-statured children and promotes their availability to families who wish to adopt such children. In addition, many average-sized parents of short children (referred to as the "little littles" within LPA) had particular concerns, and organized an auxiliary to deal with these concerns.

An LPA Foundation has been formed to obtain and distribute funds for vocational training, scholarships, and the support of medical and scientific research. A Medical Advisory Board (MAB) serves as a resource for medical care and advice. Because LPA members often participate in a variety of research projects, the MAB reviews these projects for ethical and scientific merit.

LPA members have produced some excellent reading material. *The Idea Machine* provides information about handy gadgets and daily living tips for short-statured persons. A national newsletter, *LPA Today,* and district and chapter newsletters report on matters of interest to all members. The parents of "little littles" have written a booklet entitled, *My Child is a Dwarf*; it contains pertinent information about childhood development and special adjustments.

Physicians, paramedical professionals, and families are encouraged to write directly to LPA National Headquarters, P.O. Box 633, San Bruno, CA 94066, or to the Canadian counterpart at Little People of Canada, P.O. Box 453, Abbotsford, British Columbia V2X 2Z5, Canada.

The Human Growth Foundation (HGF) was organized in 1965 by parents whose children had severe growth problems of any type. Largely through the efforts of the HGF, growth hormone therapy was made available. From its inception, the HGF has worked hard to support basic and clinical research pertaining to growth disorders. The organization recently launched a program of career starter grants for professionals involved in growth disorder research.

The HGF has also produced excellent informational booklets on growth problems such as achondroplasia, Turner's syndrome, intrauterine growth retardation, short stature, and dwarfism. These booklets are an important resource to parents and children who face the difficulties associated with short stature. Inquiries may be addressed to The Human Growth Foundation, 4607 Davidson Drive, Chevy Chase, MD 20815 (301-656-7540).

In the United Kingdom, the **Association for Research into Restricted Growth (ARRG)** was founded in 1970 to promote investigations into the basic nature of growth problems, and to serve as a self-help

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Support Groups for Families of Children With Growth Problems

continued from p. 7

organization concerned with the well-being of people with restricted growth. The ARRG has also prepared a number of excellent pamphlets dealing with growth disorders. Information may be obtained from ARRG, c/o Miss P.R. Rutt, 24 Pinchfield, Maple Cross, Rickmansworth, Hertfordshire WD3 2TP, England.

There is also the **International Association of Little People (IALP),** which was established to promote interaction between the organizations of various countries. The international organization has addresses of contact people in many countries. Those wishing information should write to Joy Cambell, International Correspondent, 5612A Hillsdale Boulevard, Sacramento, CA 95842.

Several groups have also been established for patients and their families whose short stature is associated with a specific disorder.

Although not all individuals with osteogenesis imperfecta are short in stature, they do have many medical and social problems. All types of osteogenesis imperfecta seem to be due to genetically determined collagen abnormalities. Complications include frequent bone fractures, dental anomalies, and deafness. Several lay and support groups addressing these problems have been formed. These groups and their addresses are **The American Brittle Bone Society,** 1256 Merrill Drive, Marshallton, West Chester, PA 19380; the **Osteogenesis Imperfecta Foundation, Inc.,** P.O. Box 838, Manchester, NH 03105; **Osteogenesis Imperfecta National Capital Area, Inc.,** Box 941, 1311 Delaware Avenue SW, Washington, DC 20024; and the **Canadian Osteogenesis Imperfecta Society**, Box 607, Station U, Toronto, Ontario M8Z 5Y9, Canada. All have newsletters that provide members with information about available aids, therapy, and new developments in research.

Individuals with Turner's syndrome have a special set of concerns, in addition to those associated with short stature. The **Turner's Syndrome Society** was founded to address these concerns. It has been extremely active in providing information about problems specific to patients with Turner's syndrome by producing an excellent videotape and publishing an informative newsletter every few months. A booklet prepared by the Society, *The X's and O's of Turner's Syndrome*, is excellent for patients and families. Correspondence should be addressed to The Turner's Syndrome Society, c/o Susan Charney, York University, Administrative Studies Building, 4700 Keele Street, Downsview, Ontario M3J 1P3, Canada.

The mucopolysaccharidoses and mucolipidoses are rare hereditary disorders with enzyme deficiencies in which abnormal compounds collect in the cells of various body tissues. Most of these disorders result in short stature and are associated with a variety of other problems. To promote research and public awareness, the **Society for Mucopolysaccharide Diseases** was founded. Groups have formed in the United States and Canada. They are **The MPS Society, Inc.**, 552 Central Avenue, Bethpage, NY 11714 and **The Society for MPS,** c/o Shelia Lee, 382 Parkway Blvd., Flin Flon, Manitoba R8A OK4.

This list of lay and support groups is not all-inclusive. Rather, it is intended to alert physicians to the availability of this type of resource for patients and families. Some families are hungry for information; it is wise that they be put in contact with these groups. Other families are initially resistant to joining but should be encouraged to seek information intermittently; over the long run, they will gain from the availability of reliable information and from the knowledge that they are not alone. When patients and families do become knowledgeable about rare disorders, it is important that physicians not feel threatened. Instead, they should help to put that knowledge into perspective since a lay person without a medical background can have unrealistic expectations and often needs to be reminded not to lose sight of the "whole child." On the other hand, lay groups need the support of the medical profession (and of individual physicians to serve as medical advisors) so they can work effectively in dealing with the problems associated with short stature.

Letter From the Editor

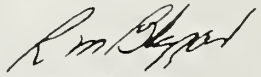
Dear Colleague:

In the four issues of *Growth, Genetics, and Hormones* published thus far, the Editorial Board has presented a number of pertinent articles as well as abstracts of special interest. We are particularly pleased that one of the abstracts that appeared in the first issue—Pseudopituitary Dwarfism Due to Resistance to Somatomedin: A New Syndrome—has elicited an "update" from Dr. Roberto Lanes of Caracas, Venezuela.

Dr. Lanes wrote to inform us that he has heard recently of two more patients with the syndrome. He and his colleagues reported one such patient in the *Journal of Clinical Endocrinology and Metabolism* in 1980 (50:485). Dr. Lanes noted in his letter that this syndrome is possibly more common than previously thought, posing a difficult problem for pediatric endocrinologists because affected children do not respond to any form of currently available therapy.

The Editorial Board thanks Dr. Lanes for his comments and encourages all of our readers to communicate with us regarding such events. We also invite you to share with us any comments you might have about specific articles or about the publication in general. We look forward to hearing from you.

Sincerely,



Robert M. Blizzard, M.D.
Chairman, Editorial Board

Effect of GH-Releasing Factor on GH Release in Children With Radiation-Induced GH Deficiency

Lustig and co-workers report five male children who had received cranial irradiation for extrahypothalamic intracranial neoplasms or for leukemia, and subsequently developed severe growth hormone (GH) deficiency. Each was challenged with supramaximal amounts of growth hormone-releasing factor (GHRF). Mean peak GH levels after GHRF rose to values higher than those evoked by levodopa or arginine (6.4 ± 1.3 ng/ml *v* 1.5 ± 0.4 ng/ml, $P<0.05$). The responses to GHRF were similar to those obtained in children with severe GH deficiency due to other etiologies. The results support the hypothesis that cranial irradiation in children can lead to hypothalamic GHRF deficiency secondary to GHRF-neuronal injury.

Lustig RH, Schriock E, Kaplan SL, et al: *Pediatrics* 1985;76:274.

Editor's comment—*These data are consistent with previous reports of diminished GH secretion after cranial irradiation for neoplastic disease. However, they show pituitary responsivity to GHRF and point toward the hypothalamus as the site of injury. The five patients with severe GH deficiency represent a rather small subset of those who have had cranial irradiation. It would be of interest to test a large number of long-term surviving children who had received cranial irradiation with submaximal amounts of GHRF to determine sensitivity as well as efficacy. Additional data—such as those from Blatt and co-workers (J Peds 1984;104:182) assessing the intrinsic secretory pattern of GH—would round out this study to define the neurosecretory system alteration for the GH "system" following a single protocol of cranial irradiation.*

Skeletal Age Changes in Puberty

A study by J.M.H. Buckler of Leeds, England, was conducted in 34 Leeds schoolboys, 10.1 to 11.4 years of age. Height measurements were taken every four months, and bone-age x-rays were obtained annually for four to five years. Growth velocity and skeletal velocity using the Tanner Whitehouse 2 (TW2) method to evaluate skeletal maturation were compared to ascertain if skeletal maturation progresses consistently year by year through adolescence. The data indicate that skeletal ages advance more rapidly than chronological ages during adolescence and that there is a direct relationship between skeletal velocity and growth velocity. Peak skeletal age velocity advances almost simultaneously with peak height velocity (13.7 ± 0.8 years *v* 14.3 ± 1.0 years).

The TW2 standards for bone ages, when established, were obtained using groups of children at various ages. These children were x-rayed once and, therefore, the standards do not take into account this rapid advancement of bone age at the time peak height velocity occurs.

In males who are growing rapidly, bone-age determinations that are done serially will advance at rapid rates. If this fact is not recognized, errors in interpretation may be made. Late developers will initially show a relative retardation of bone age, but their skeletal age will catch up when puberty ultimately occurs. In monitoring treatment, *physicians sometimes attribute the rapid changes in skeletal age* that occur at this time to incorrect treatment, when in fact these changes can be readily explained by the patient's stage of puberty.

Buckler JMH: *Arch Dis Child* 1984; 59:115.

Editor's comment—*We have all observed that, in certain patients, skeletal maturation occurs very rapidly and out of proportion to the chronological time that has passed. Dr. Buckler has supplied an explanation for at least some of these observations.*

Pituitary Dwarfism in a Patient With Circulating Abnormal GH Polymers

Valenta et al describe the growth pattern of a short 14-year old boy, the son of relatively short parents. His height and weight were average for a 10-year-old, and he had growth failure for at least the previous three years, growing between 1.5 and 3.5 cm/yr. Despite Tanner stage III development of the genitalia and pubic hair and circulating sex-hormone levels corresponding to this stage of sexual development, he had not yet shown a pubertal growth spurt. The physical examination, blood chemistry analyses, and circulating pituitary and endocrine target organ hormone concentrations were normal. The responses to all pharmacologic stimuli for growth hormone (GH) secretion were normal (peak GH: 9.6 to 36 ng/ml) and the somatomedin C (SmC) concentration was 1.7 U/ml. There was a marked acceleration of growth rate during exogenous GH therapy.

The circulating GH and the fractionated components (gel chromatography) were subjected to various immunoassays and bioassays to determine their activities. Using the IM-9 continuous cell line of cultured human lymphocytes (receptor assay, RRA), these investigators found an RRA/radioimmunoassay of 0.5 and the bioassayable activity (Nb-2 cell lactogenic assay) reduced by 25%. On column chromatography, the usual three peaks of GH species were noted—"Big-Big" [85,000 Daltons, (?) tetramer], "Big" [45,000 Daltons, (?) dimer], and "little" [20,000 Daltons, monomer]—but were present in unusual proportions—60% to 90% GH polymers rather than the more usual

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14% to 40% in plasma. Further physical analysis revealed that the units of the polymers were joined by disulfide (covalent) linkage rather than the more usual noncovalent ("stuck together") forces.

Valenta LJ, Sigel MB, Lesniak M, et al: *N Eng J Med* 1985;312:214.

Editor's comment—*The chemical analysis of the circulating GH species is very thorough and makes a very convincing case for a distinct abnormality in the physical and chemical properties of GH. However, it is less certain whether these abnormalities were the cause of this young man's shortness.*

From the few growth points measured early on, it seems likely that this boy did not have growth failure before the age of 8 or 9 years. This pattern would be distinctly unusual for a congenital growth problem. In addition, the baseline SmC concentration was at the upper limit of normal—1.7 U/ml—rather than subnormal, which would be the case if these molecular species were unable to cause the liver to produce SmC. The IM-9 cell receptor GH activity was low with respect to the immunoassay potency, but no mean and standard deviations are given for those GH components in normal serum. Could these values merely represent the "tail" of Gauss? Finally, the Nb-2 cell bioassay results reflect the lactogenic activity of circulating human growth hormone (hGH) (after immune precipitation of the other lactogen, prolactin). Although the results may be low (no mean and standard deviations are given for normals), this activity may not reflect the growth-promoting activity of hGH. What clearly needs to be done with the GH molecules in this patient's serum is to concentrate them immunologically before testing the mixed and/or separated components in a bioassay for growth in hypophysectomized mice or rats or in the tibial-line assay. In summary, although this patient most probably has an abnormality in distribution of GH polymers, it is doubtful that the hypothesis of an abnormal circulating GH molecule of diminished biological activity has been proven.

Fibrochondrogenesis—A Lethal, Autosomal Recessive Chondrodysplasia With Distinctive Cartilage Morphology

The lethal neonatal osteochondrodysplasias are a heterogeneous group of disorders that can be distinguished from each other by radiologic and histopathologic criteria. Fibrochondrogenesis, a neonatally lethal, short-limbed skeletal dysplasia, was first described in 1978 in a single patient who was the offspring of a consanguineous mating. This disorder was named "fibrochondrogenesis" because of a distinctive fibrosis of the growth plate cartilage. In these two articles, four more patients with this syndrome are described and the clinical, radiographic, and morphologic features are defined.

The main clinical features were short-limbed, rhizomelic-type neonatal dwarfism, a relatively large head, a round flat face with prominent eyes, cleft palate (in two of four patients), and a small chest. All four were sporadic, nonconsanguineous cases.

Radiographically, the long bones were short and dumbbell shaped, with broad metaphyses. The ribs were short and cupped. The iliac bones were small and rounded. Diffuse platyspondylia was present, with superior-inferior clefting defects and pear-shaped bodies.

Histological examination of chondro-osseous tissue revealed peculiar pathognomonic abnormalities of the cartilage. The resting cartilage was hypercellular, with round or spindle-shaped fibroblastic-appearing cells. The matrix appeared to be fibrous, with dense septae. At the growth plate, the cells were clustered in irregular nests within a fibrous matrix. The bone appeared normal in structure. Transmission electron microscopy of the cartilage revealed a fibrous matrix surrounded by round or fibroblast-like chondrocytes. The fibrous-appearing matrix was composed of thick-banded, densely packed collagen fibers. Proteoglycan granules were deficient in these areas.

These findings suggest either a defect of Type II collagen synthesis or structure, or an abnormality in the aggregation of collagen fibers secondary to a deficiency or abnormality in proteoglycans. Although this disorder was first distinguished on the basis of the peculiar morphologic cartilagenous abnormalities, the radiographic features have now been recognized as quite distinctive.

Whitley CB, Langer LO, Ophoven J, et al: *Am J Med Genet* 1984;19: 265-275; and Eteson DJ, Adomian GE, Ornoy A, et al: *Am J Med Genet* 1984;19:277-290.

Editor's comment—*The 1983 Conference for International Nomenclature of Constitutional Disease of Bone (Paris) enumerated ten lethal osteochondrodysplasias identifiable in the newborn period. Several new osteochondrodysplasias are identified each year. An accurate diagnosis must be made to provide meaningful prognostic information and appropriate genetic counseling. The differential diagnosis of these disorders depends on clinical, radiographic, and/or morphologic criteria, since their basic biochemical defects have not yet been elucidated.*

Most of the severe neonatal disorders can be diagnosed prenatally by careful serial ultrasound examinations during the second trimester.

Late-Onset Adrenal Hyperplasia in Hirsutism

The investigators studied the incidence of late-onset adrenal hyperplasia as a cause of hirsutism, its association with the major histocompatibility complex, and its clinical expression. Their patient population included 400 women seen for hirsutism. Twenty-four (6%) were found to have late-onset adrenal hyperplasia.

Nonclassical, late-onset forms of adrenal hyperplasia, in which sexual ambiguity is not present at birth but virilization occurs during childhood or after puberty, have been described. However, these late forms are extremely variable in age at appearance, in degree of hyperandrogenism, and in association with abnormalities of the menstrual cycle. An elevated basal plasma 17-hydroxyprogesterone (17-OHP) level—especially its dramatic elevation after adrenocorticotropic hormone (ACTH) stimulation—leads to the diagnosis of "partial" adrenal 21-hydroxylase deficiency.

All 400 women had ACTH stimulation tests in which 17-OHP and adrenal androgens were measured. In addition, the 24 identified as having late-onset adrenal hyperplasia due to 21-hydroxylase deficiency had human leukocyte antigen (HLA) typing since this form, like the classical form, is linked to the major histocompatibility complex. The families of these 24 patients underwent HLA typing as well.

Basal cortisol concentrations did not differ from normal values, but the increase after ACTH was significantly lower than normal. By contrast, 17-OHP levels were higher than normal and strikingly increased after ACTH. Plasma androstenedione was high in all but three patients and plasma testosterone levels, although often elevated, were normal in nine patients. Urinary excretion of 3α-androstenediol was higher than normal in most cases.

HLA typing showed HLA B-14 in 75% of the index patients, but in only 11.7% of a control population. AW-33, B-14 was 40 times more common in the patients. The family members who had HLA typing were divided into three groups: HLA identical, one haplotype in common (heterozygotes), and no haplotypes in common (normal). As expected, the basal and post-ACTH 17-OHP concentrations in the heterozygotes were intermediate between those values in the normals and those in the homozygotes.

Kuttenn F, Couillin P, Girard F, et al: *N Eng J Med* 1985;313:224.

Editor's comment—*This study represents the accumulation of large amounts of interpretable data on hirsute women and their families. The results indicate the utility of the ACTH stimulation test as part of the diagnostic evaluation of hirsute women and, by implication, in children of both sexes with premature andrenarche.*

More importantly, this study points to the remarkable variability in the expression of androgen excess in these women and their families. Hirsute women with similar androgen profiles can have totally dissimilar menstrual alterations. Siblings with HLA-identical haplotype may or may not have the same androgen profile or clinical presentation. The facts that both symptomatic and asymptomatic forms of late-onset adrenal hyperplasia occur in the same family, that they are biochemically identical and are linked with the same HLA antigens, and that they are strongly associated with HLA B-14, suggest that the genetic mutation in the symptomatic and asymptomatic forms is the same.

The consideration of late-onset adrenal hyperplasia should be mandatory not only in the hirsute adolescent and adult, but also in the child with premature andrenarche.

Use of Plasma SmC/IGF-1 Measurements to Monitor the Response to Nutritional Repletion in Malnourished Patients

The purpose of this study was to evaluate the usefulness and sensitivity of somatomedin C/insulin-like growth factor I (SmC/IGF-I) concentrations as an indication of short-term nutritional rehabilitation in malnourished patients. Six malnourished adults were studied during a period of ten to 16 days of parenteral or enteral nutritional therapy. These patients had a variety of gastrointestinal disorders that led to malnutrition. A statistically significant increase in plasma SmC/IGF-I concentrations was reported from a baseline (mean ± SD) of 0.67 ± 0.15 U/ml to 0.93 ± 0.38 U/ml after two days of refeeding. By the 16th day of nutritional therapy, the SmC/IGF-I had fallen to 1.28 ± 0.49 U/ml from a peak of 1.80 ± 0.44 at day 10. All patients were in positive nitrogen balance throughout the duration of the study. In contrast, the levels of prealbumin, transferrin, and retinal-binding protein did not reflect significant changes.

In summary, the findings of this study suggest that plasma SmC/IGF-I is a more sensitive indicator of improved nutritional status during short-term nutritional rehabilitation in malnourished patients than other plasma proteins that are frequently used to assess nutritional status.

Clemmons DR, Underwood LE, Dickerson RN, et al: *Am J Clin Nutr* 1985;41:191.

Editor's comment—*This paper demonstrates the validity of SmC/IGF-I levels as an indicator of short-term nutritional status. This may, therefore, be useful in evaluating the response to treatment in various forms of nutritional dwarfism, as well as the compliance of the patients with dietary intervention.*

MEETING CALENDAR

January 17-19 American Diabetes Association 33rd annual postgraduate course. The Waldorf-Astoria, New York, New York. Contact: American Diabetes Association, 2 Park Avenue, New York, NY 10016 (212-683-7444)

February 4-7 Joint Meeting of the Western Section of the American Federation of Research and the Western Society for Pediatric Research. Various locations in Carmel, California

February 6-8 Canadian College of Medical Genetics. Spencer Hall, London, Ontario. Contact: Canadian College of Medical Genetics, Alberta Children's Hospital, 1820 Richmond Road SW, Calgary, Alberta T25C7

April 12-17 American Academy of Pediatrics. Spring Session. Orlando, Florida. Contact: American Academy of Pediatrics, Division of Continuing Education, P.O. Box 927, Elk Grove Village, IL 60067 (312-228-5005 or 800-433-9016)

April 28-30 1st International Symposium on Serum Hormone-Binding Proteins. Contact: Dr. M.T. Forest, Insermu 34, Hopital Debrousse, F-69322, Lyon, Cedex 05, France

May 6-9 American Pediatric Society/ Society for Pediatric Research. The Sheraton Washington Hotel. Washington, D.C.

May 9 Annual Meeting of the Lawson Wilkins Pediatric Endocrine Society. The Sheraton Washington Hotel, Washington, D.C. Contact: Dr. Salvatore Raiti, Secretary, LWPES, Suite 501-9, 210 West Fayette Street, Baltimore, MD 21201 (301-837-2552)

June 8-11 March of Dimes Birth Defects Symposium. Westin Bellevue-Stratford, Philadelphia, Pennsylvania

June 22-24 46th Annual Scientific Sessions of the American Diabetes Association. Anaheim Convention Center, Anaheim, California. Contact: American Diabetes Association, 2 Park Avenue, New York, NY 10016 (212-683-7444)

June 25-27 65th Annual Meeting of The Endocrine Society. Anaheim Convention Center, Anaheim, California. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-530-9660)

Robert M. Blizzard, M.D.
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